Abstract N°: 290

Birt-Hogg -Dube Syndrome, a new familial case

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Introduction & Objectives:

Birt-Hogg-Dubé syndrome (BHDS) is an infrequent genetic syndrome mainly defined by lung bullae and kidney neoplasms, trichodiscoma-fibrofolliculoma facial lesions are the most common skin expression.

Materials & Methods:

A woman 45 y.o presented several whitish millimetrical papules located over cheeks and nose dorsum gradually increasing in size in last 15 years, she referred similar lesions in mother and aunt (mother’s sister) suggesting an autosomal dominant pattern of transmission. A biopsy was performed obtaining trichodiscoma diagnosis what oriented to BHDS. No lung or kidney disease previously known, she presented familial history of colonic benign polyps. A body CT was performed observing predominantly basal located lung bullae 15-mm of maximum size; no kidney benign nor malignant lesions but an adrenal gland functional benign nodule was observed. A colonoscopic exploration was performed in search of colonic adenoma observed in BHDS, without significant findings. We also asked for a thyroid ultrasound scan that was completely normal.

With all this findings we asked for a genetic study that evidenced heterozygous FLCN gene mutation c.1351-1356delinsA (p.Pro451Argfs*3) confirming BHDS on this family.

All affected members are being followed with kidney and thyroid ultrasound, colonoscopic exploration and lung radiography every 1-3 years without further findings to date.

Results:

BHDS is an autosomal dominant syndrome caused by FLCN gene mutation. Its cutaneous manifestations include trichodiscoma-fibrofolliculoma lesions appearing from 20-25 y.o., an hamartomatous proliferation consisting on tiny flesh-colored mainly facial papules, related to hair follicle, and that histologically show unencapsulated, elliptical, loosely woven admixture of reticulin-collagen-elastic fibers and mucopolysaccharides.

There is an association to internal disease especially renal tumors, frequently bilateral, including oncocytoma and chromophobe or papillary renal cell carcinoma. Also lung diseases are described including spontaneous pneumothorax, lung cysts and bullous emphysema. There is an uncertain association to intestinal polyps and intestinal malignancy. Other manifestations described are thyroid and parathyroid benign and malignant lesions, and cutaneous findings as lipomata or conective tissue nevi

Conclusion:

We present a familiar case of BHDS gathering several typical manifestations including autosomal dominant genetical transmission pattern, dermatopathologically confirmed multiple cutaneous trichodiscomas and lung basal bullae; the genetic study confirmed FLCN gene mutation what supports the diagnosis. We haven’t found any renal or thyroid mass and colonoscopic exploration has been normal to date. As a curious fact a functional benign adrenal nodule was detected and is under observation (few cases of adrenal oncocytoma have been described in
Incidence and prevalence of 73 different genodermatoses: a nationwide study in Sweden

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Introduction & Objectives:

The incidence and prevalence of most genodermatoses are rough estimates.
The relative amounts of various hereditary skin diseases, and the health care usage of patients are largely unknown.
The purpose of this retrospective registry-based cohort study is to report the incidence and prevalence of genodermatoses in the Swedish population and to analyze the associated health care usage of these patients.

Materials & Methods:

Patients diagnosed with genodermatoses between the years 2016 to 2020 were retrieved from the patient registry of our hospital. Clinical data were extracted from medical records and used to verify the diagnoses recorded in the National Patient Registry (NPR) and calculate the positive predictive value for each diagnosis. The NPR was also searched for International Classification of Diseases, Tenth Edition (ICD-10) codes Q80-82 and Q84 from 2001 to 2020. Physicians’ appointments at dermatology departments were retrieved, and the incidence and prevalence of each diagnosis was calculated based on the nationwide cohort.

Results:

The local cohort included 297 patients with 36 unique genodermatosis diagnoses in ICD-10 blocks Q80-Q82, Q85 and Q87. The verification of diagnoses in the NPR revealed positive predictive values of over 90% for the whole group of genodermatoses. The search of the NPR for ICD-10 blocks Q80-Q82, and Q87.5 yielded 13,318 patients with 73 unique diagnoses, the most common of which were ichthyoses (n=3,341; 25%), porokeratosis (n=2,277; 17%), palmoplantar keratodermas (n= 1,754; 13%), the epidermolysis bullosa group (n=1011; 7%), Darier disease (n=770; 6%) and Hailey-Hailey disease (n=477; 4%).
Overall, a total of 149,538 outpatient visits were registered, averaging 4.6 visits per patient.

**Conclusion:**

The present study reports incidence and prevalence of 73 genodermatoses and provides a resource for the epidemiology of genodermatoses. Data from the NPR can be used for further epidemiological studies of this disease group in the future.
Abstract N°: 659

ADAM17, a new pathogenic gene for autosomal dominant hypotrichosis.

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Introduction & Objectives:

Hereditary hair loss in human is a group of clinically and genetically heterogeneous disorders, which are often characterized by sparse or complete absence of hair on the scalp and other body parts. During the past 20 years, 11 causative genes for non-syndromic forms of hypotrichosis have been identified. Besides these findings, the causative genes in these families have yet to be discovered and the molecular mechanisms underlying hypotrichosis have not been fully disclosed.

Materials & Methods:

We performed a genome-wide linkage analysis approach by polymorphic microsatellite markers and to find candidate pathogenic genes. The whole exome sequencing and Sanger sequencing was performed to confirmed the variants. Knock-in mice was constructed to mimic the hair loss. The electron microscopy was used to reveal the hair structure. Immunostaining and the whole-mount immunostaining was performed to explore the malformation of the hair follicles. We used proteomics to hint the intrinsic effects resulting from the loss of Adam17.

Results:

We identified a new pathogenic gene (ADAM17) and its mutation site (p.D647N) associated with hereditary hypotrichosis with woolly hair. By studying the affected family and ADAM17-mutation knock-in mice, we find that ADAM17 plays an important role in hair follicle stem cells. ADAM17 mutation leads to the depletion of hair follicle stem cells, abnormal hair follicle structure and sparse hair. Furthermore, mutations in the ADAM17 gene result in decreased expression of self-proteins at the post-transcriptional level, increased ubiquitination levels, and significant downregulation of the Notch signalling pathway.

Conclusion:

In this report, we link a core molecular to hair loss, thus adding another specific factor in the complexity of hair growth. We found a crucial site of ADAM17 which regulated self-proteins ubiquitination. Furthermore, we elucidate the mechanism of ADAM17-Notch signalling axis regulation in hair follicle development, providing potential targets for clinical diagnosis and treatment of hair loss.
Pulsed dye laser for facial erythema in Netherton syndrome

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Introduction

Netherton syndrome (NS) is a rare autosomal recessive disorder characterized by a triad of atopic diathesis, ichthyosis linearis circumflexa (ILC) and hair shaft abnormalities. It is caused by pathogenic variants in the SPINK5 gene, also known as LEKTI (lymphoepithelial Kazal type 5 related inhibitor). There is no satisfactory treatment currently available for NS.

Results

A 34-year-old male patient with NS presented with persistent erythema of the face. This manifestation of NS had the most important impact on our patient’s emotional well-being in adult life, leading to embarrassment and lower self-esteem. Skin examination revealed serpiginous erythematous plaques with double-edge circumferential scales on arms and trunk, named ILC. In 2006, genetic testing revealed a mutation in the SPINK5 gene, confirming diagnosis of NS.

Previously, topical 0.33% brimonidine gel on the whole face resulted in partial resolution of redness for 5 hours. Topical corticosteroids, topical calcineurin inhibitors and skin moisturizers were used on the body, with good effect. In a study where the protease inhibitor LEKTI cream was applied on his body, the erythema didn’t change.

Due to the significant impact of facial erythema on the quality of life (QOL), he consented to Pulsed dye laser (PDL) treatment. PDL was performed on the face and improvement of erythema was observed after 1 session. The treatment was performed with the smallest purpuragenic fluence according to individual response. Post laser purpura and facial swelling faded after 1-2 weeks. A 595nm Candela PDL system (Vbeam Perfecta, Syneron Candela Corporation, Boston, Mass., USA) was used. First, a test spot with a fluence of 15.5J/cm², 7mm spot size, and a pulse width of 20ms was used.

Based on the biological response of the test area, the fluence was adjusted up or down. In the consecutive treatments, following laser settings were used: the spot size varied between 5-7mm, the pulse width varied between 10-20ms and the fluence varied between 6.5-17J/cm². Treatment fluence was selected to induce faint transient purpura at the purpura threshold, but no persistent purpura was induced to avoid post-laser downtime. Non-contact cooling was used to minimize epidermal damage. Laser pulses overlapped by 10% to have a uniform result.*

Initially, we performed 3 PDL treatments with good response. The treatment interval was between 3-8 months. The patient reported a marked improvement on his QOL due to reduced facial erythema, especially during physical exercise. Since the facial erythema gradually came back after 3 years, he wanted to repeat PDL treatment and we performed 2 PDL sessions at 2-months interval.

Discussion

Previous studies show that facial erythema associated with rosacea, has a negative impact on psychological and emotional health and those patients are often affected by social stigma. 595nm PDL is the gold standard to treat congenital and acquired vascular skin conditions as port-wine stain, infantile hemangioma, Morbus Osler Rendu.
syndrome and telangiectatic rosacea.

The biophysical principle of PDL is selective photothermolysis. The laser light of 595nm PDL is selectively absorbed by oxyhemoglobin and converted to heat, which causes heat damage and necrosis of the vessel wall.

This is the first report of PDL to treat persisting facial erythema in NS. PDL proved to be a safe, effective and non-invasive modality with short downtime. The effect was long-lasting and improved QOL in our patient.
Phacomatosis pigmentokeratotica and hypophosphataemic rickets: a very rare association.

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Introduction & Objectives:

Epidermal nevus syndrome (ENS) is the association of an epidermal nevus and extracutaneous anomalies including: neurological, ophthalmological and skeletal defects.

Phacomatosis pigmentokeratotica (PPK) is a new ENS (1) defined by the association of nevus spilus (NSp) arranged in a flag-like pattern and sebaceous nevus (SN) following Blaschko lines (2) with the exceptional association of extra-cutaneous abnormalities.

We report a rare case of PPK associated with hypophosphatemic rickets (HR).

Materials & Methods:

Results:

Observation: A 5-year-old boy from healthy consanguineous parents without family history of skin or bone disease presented with unusual cutaneous lesions made of SN of the scalp, face, back and a keratinocytic nevus of the right thigh following Blaschko lines, associated with 03 bald areas of the scalp, one of which is overtaken by a NSp, the latter also takes the right trunk and the back. Those cutaneous manifestations allowed us to make the diagnosis of PPK and to look for the extra-cutaneous anomalies that may be associated with it.

On clinical examination, we found: deformity of the upper and lower right limbs. The parents reported spontaneous fractures of the right arm and leg. This deformity was associated with retarded growth in stature and weight. On the bone X-rays there were signs of rickets (irregular appearance and widening of the metaphyses, demineralization, multiple fractures). Laboratory studies showed: low phosphatemia, high alkaline phosphatase, normal PTH and normal 1-25 OH vitamin D (after supplementation), concluding with the diagnosis of hypophosphatemic rickets (HR), the child was put on calcitriol and phosphate supplements.

Neurological and ophthalmological examination revealed no abnormalities.

These data were consistent with the very rare diagnosis of PPK associated with HR.

Conclusion:

Discussion: Phacomatosis pigmentokeratotica is an epidermal nevus syndrome. It is defined by the association of nevus spilus (NSp) and sebaceous nevus (SN), as found in our patient. It is a rare entity with, to our knowledge, only 30 cases reported. (5) It is due to a post-zygotic mutation in the HRAS pathway of a multipotent cell. (6) Identical RAS mutations have been identified in skin and bone. (4)

Extracutaneous involvement of PPK includes malformations of the nervous, skeletal, and endocrine systems. (2) It was hypophosphatemic rickets (HR) that was diagnosed in our little boy.

HR rarely associates with PPK. To our knowledge, only 20 cases have been reported in the literature (8), in addition to ours. This type of rickets is secondary to a defect in the reabsorption of phosphorus in kidneys due to
an excessive secretion of the FGF23 hormone (secondary to the mutation of the HRAS gene). This hormone inhibits the expression of 1-alpha hydroxylase, necessary to the conversion of 25-hydroxy-vitamin D into 1,25-dihydroxyvitamin D.

The treatment of HR is based on phosphate in solution as well as active vitamin D. (7), which our patient received.

Conclusion: We report a new case of the very rare association of PPK and HR and we highlight the need to search for rickets in those patients in order to treat it early and thus avoid the complications that can result from it.
Overlap of Familial Mediterranean Fever and Autoinflammatory Phospholipase Cγ2 (PLCγ2)-Associated Antibody Deficiency and Immune Dysregulation in a Turkish Patient

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Introduction & Objectives: Autoinflammatory diseases represent a group of inherited disorders with genetic defects of innate immunity leading to uncontrolled systemic or organ-specific inflammation. Although familial Mediterranean fever (FMF) is a common one that is usually seen in Mediterranean and Middle Eastern regions, autoinflammatory phospholipase Cγ2 (PLCγ2)-associated antibody deficiency and immune dysregulation (APLAID) is extremely rare. Herein, we report the first case of overlap of FMF and APLAID in a patient.

Materials & Methods: A 36-year-old male patient presented to our dermatology outpatient clinic with waxing and waning course of widespread multiple pustular eruptions since childhood and severe aggravation for the last month. He had no abdominal pain or fever attacks. He was diagnosed with bronchiectasis and emphysema for about ten years. He began to have episodes of arthritis of the foot and knee joints in early infancy. He had a diagnosis of FMF, and he had been put on colchicine therapy when he was 19. Heterozygous M694V and M680I mutations were detected in the MEFV gene. Colchicine provided the relief of arthritis; however, it did not resolve attacks of pustular eruption.

Results: Histopathological examination of pustules showed neutrophilic exudation, and microbial cultures were negative. High levels of C-reactive protein and erythrocyte sedimentation rate, mild lymphopenia, mild low IgM levels and decreased CD4/CD8 ratio were detected. Chest X-ray showed increased linear opacities in the bilateral upper zones, flattening in both diaphragms and effacement of their borders. Systemic corticosteroid therapy provided rapid regression of all skin lesions. Genetic analysis confirmed a heterozygous mutation, c.2120C>A (p.S707Y), within the PLCG2 gene. Daily 100 mg anakinra therapy provided regression of subsequent relapse of all pustules within two months. After the third month of treatment, the opacities seen on the chest X-ray disappeared and the diaphragm borders became clear. In a 6-month follow-up, the patient experienced only one relapse of pustular eruption, which resolved with short-term low-dose systemic corticosteroid treatment.

Conclusion: APLAID overlap with FMF should be considered in patients with recurrent pustular eruptions.
A cohort of Tunisian patients with Netherton syndrome: Molecular signature and Genetic investigations

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Introduction & Objectives: Netherton syndrome (NS) is a rare autosomal recessive genodermatosis, it is actually defined by the clinical triad characterized by an atopic manifestation, scaly erythroderma (SE) or Ichthyosis Linearis Circunflexa (ILC) and a specific Hair shaft abnormality known as Trichorrhexis invaginata (TI). NS is caused by loss of function mutations in SPINK5 gene encoding kazal-type serine protease inhibitors (LEKTI) highly expressed in the stratified epithelium and significantly in the granular layer of the epidermis. We aim to analyze NS in Tunisian patients by examining their clinical, biological, histological, and genetic features, and identifying therapeutic targets through analysis of the inflammatory signatures in their skin.

Materials & Methods: Our study focused on 17 patients from 13 unrelated Tunisian families with NS, who were referred to our department for genetic confirmation of their diagnosis.

Results: The age of onset was neonatal in all cases. Clinical examination at birth showed congenital ichthyosiform erythroderma in 13 cases, bullous in only one case. The scalp was the site of a diffuse scaly shell. TI, as well as atopic dermatitis, was noted in all patients. LEKTI immunostaining was negative in all patients. Immunostaining of inflammatory cytokines showed massive neutrophil and mast cell infiltrates in the lesion and non-lesion skin in both NS subtypes. A remarkable expression of Th2 cells in the dermis for the two subtypes was noted.

Next generation sequencing and Sanger sequencing of the SPINK5 gene identified a known homozygous c.1888-1G>A mutation at the splice acceptor site of exon 21 in 7 patients. A homozygous c.2264dupA mutation at exon 24 was present in 2 patients. A homozygous c.2471delAAGA deletion in 2 related patients. A previously described homozygous c.2441+3delCAGT mutation at the splice donor site of exon 25 in one patient. A new nonsense pathogenic variant homozygous c.217G>T at exon 4 in 2 patient. Furthermore, the last patient was compound heterozygous for a new c.2302G>T mutation, and a deep intronic variant. Haplotype analysis in NS patients by genotyping seven microsatellite markers flanking the SPINK5 gene indicates that all carriers of the c.1888-1G>A mutation have the same haplotype.

Conclusion: We report the largest cohort of Tunisian patients with NS, including 7 patients presenting the same mutation in favour of a founder effect. We have also identified 5 pathogenic variants, in which 2 new variants, in 10 patients. We hypothesize that the existence of intra and inter-familial phenotypic differences between individuals carrying the same SPINK5 mutation suggests the interference of other epigenetic and environmental genetic factors in the expression of NS.
Painful leiomyomas in hereditary leiomyomatosis with renal cell cancer, should they all be excised?

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Introduction & Objectives:

This 36 year old lady presented to our department with multiple red papules on the anterior surface of both her legs and her right arm, starting from the age of 14. She had had a leiomyoma excised previously elsewhere and a left nephrectomy for a multicentric oncocytoma aged 11. She was concerned with the cosmetic appearance and the burning pain that she gets from the lesions, particularly in winter. Her father suffered with similar lesions affecting his arms.

Materials & Methods:

Genetic testing confirmed deletion of one copy of the fumarate hydratase gene and a diagnosis of hereditary leiomyomatosis with renal cell cancer (HLRCC) was made. Surveillance with an annual abdominal and pelvic MRI has been recommended by the geneticist. Her most recent scan has revealed multiple longstanding unchanged cysts in her remaining right kidney, but no uterine abnormalities.

Results:

The most troublesome skin lesions have been removed by punch excision, most recently two on the abdomen and one on the right thigh. Given the number of lesions, this would not be a feasible treatment option for all the painful lesions. Treatment with nifedipine 10mg TDS was commenced in December 2022 and has had a positive effect with complete resolution of pain.

Conclusion:

HLRCC, also known as Reed Syndrome, is an autosomal dominant inherited condition characterised by uterine and cutaneous leiomyomas and renal cell carcinoma. Cutaneous leiomyomas, which tend to be multiple in HLRCC, are benign smooth muscle tumours ranging from 2 to 20mm in size. Patients can complain of pain which can be triggered by pressure, cold temperatures, strong emotion, light touch or can occur spontaneously. Uterine leiomyomata are present in almost all females with HLRCC and develop from the age of 25-40 years old1, although our patient has not developed them to date. Renal cell carcinoma (RCC) occurs in approximately 20-30% of individuals with HLRCC. Most commonly they are type 2 papillary RCC, unilateral and aggressive2. The diagnosis of HLRCC can be considered with 1 major or 2 minor criterion1. Major criteria include: Multiple leiomyoma with at least one histologically confirmed. Minor Criteria include: Early onset (<40 years) papillary type 2 renal tumours, solitary cutaneous leiomyoma and family history of HLRCC and uterine leiomyomas diagnosed before the age of 40. FH is the only gene known to be associated with HLRCC and mutations in FH are diagnostic.

Management includes identification and screening of at risk individuals for RCC2 and symptomatic relief for the cutaneous leiomyomas. Surgical excision is the treatment of choice for appropriate isolated lesions1. There is no consensus over optimal medical treatment; the use of nifedipine, doxazosin, hyoscine, and nitroglycerin has been reported. These work based on the principle of reducing smooth muscle contraction1. Other treatments such as gabapentin have also been used to control pain1.

Our case highlights the success of using nifedipine for alleviating pain associated with leiomyomas. This rare
syndrome should be considered in patients presenting with leiomyomas so testing and surveillance can be initiated.


Genotype-phenotype correlation in Junctional Epidermolysis Bullosa: novel approaches for severity prediction and characterisation

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Introduction & Objectives:

Junctional epidermolysis bullosa (JEB) is a rare autosomal recessive genodermatosis characterised by mucocutaneous cleavage within the lamina lucida of the basement membrane zone. A wide range of JEB phenotypes exist with substantial variation in severity and characteristics. Current genotype-phenotype paradigms are insufficient to accurately predict JEB subtype and characteristics from genotype, particularly for splice site mutations, which account for over a fifth of disease-causing mutations in JEB. This study evaluated genetic and clinical findings from a JEB cohort, investigating genotype-phenotype correlations through bioinformatic analyses and comparison with previously reported mutations.

Materials & Methods:

Mutations were identified through Sanger and whole-exome sequencing. Splice site mutations were analysed using SpliceAI, a state-of-the-art artificial intelligence tool which examines 10,000nt of flanking sequence around a mutation to predict the exact location of cryptic splice site activation and/or exon skipping. A dedicated JEB deep phenotyping tool was developed to systematically examine the clinical features of JEB individuals.

Results:

Eighteen unique mutations in LAMB3, LAMA3, LAMC2 or COL17A1 were identified from seventeen individuals (thirteen homozygotes and four compound heterozygotes). There were seven cases of severe JEB, nine intermediate JEB and one laryngo-onycho-cutaneous syndrome. Seven mutations were novel, and mutations in LAMB3 included five splice site mutations (Table 1).

For Case 1 (c.2701+1G>A/c.2701+1G>A) and 2 (c.565-2A>G/p.R972X), SpliceAI predicted novel out-of-frame transcripts containing premature termination codons (PTCs) following aberrant splicing, which correlated with these individuals’ severe JEB phenotypes. An in-frame transcript with 27 additional nucleotides was predicted for Case 3 (c.943+2T>C/p.R569X) secondary to cryptic splice site activation within intron 9. This likely ameliorated severity, explaining her mild intermediate JEB phenotype with minimal skin involvement.

The exact out-of-frame transcripts predicted by SpliceAI were confirmed for Case 4 (c.298+5G>C/c.298+5G>C) and 5 (c.629-12T>A/p.W1040X) by reviewing RT-PCR data. Two additional in-frame transcripts not predicted were found to be produced in low quantities. It is likely that these in-frame transcripts generated partially functional protein, alleviating JEB severity to a degree and explaining their intermediate JEB phenotypes.
All severe JEB cases had complete lack of laminin-332 immunoreactivity with immunofluorescence (GB3 antibody, Figure 1). In contrast, this was only partially reduced for Case 3 and 4 (intermediate JEB), who both had in-frame transcripts predicted or produced from splice site mutations.

Deep phenotyping was completed for all intermediate JEB cases and demonstrated substantial variation between individuals (Table 2).

**Conclusion:**

This study expands the JEB genomic landscape and is consistent with previous reports where a number of cases have milder than expected phenotypes according to classical genotype-phenotype correlation paradigms. AI tools show potential for predicting functional effects of splice site mutations and may identify candidates for confirmatory laboratory investigation. Investigation of RNA transcripts in selected cases will help to further elucidate genotype-phenotype correlations for novel mutations.

**Table 1:** SpliceAI predicted resultant transcripts from splice site mutations

<table>
<thead>
<tr>
<th>Case</th>
<th>Mutation</th>
<th>Outframe prediction</th>
<th>Inframe prediction</th>
<th>Predicted outcome</th>
<th>JEB subtype</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Homozygous c.376T&gt;T (p.K126X)</td>
<td>Out-of-frame exon 18 skipping</td>
<td>30kbp deleted from exon 18</td>
<td>Both exons out of frame</td>
<td>Severe</td>
</tr>
<tr>
<td>2</td>
<td>Heterozygous c.365-26C&gt;T (p.R95*)</td>
<td>Out-of-frame exon 7 skipping</td>
<td>11kbp included from frame 0 (including UAG PTC in U94-40)</td>
<td>Frameshift, frameshift with frameshift</td>
<td>Severe</td>
</tr>
<tr>
<td>3</td>
<td>Heterozygous c.1170C&gt;T (p.R388X)</td>
<td>Out-of-frame exon 9 skipping</td>
<td>27kbp included from frame 0</td>
<td>Frameshift, frameshift with frameshift</td>
<td>Intermediate</td>
</tr>
<tr>
<td>4</td>
<td>Homozygous c.288-5G&gt;C</td>
<td>Out-of-frame exon 1 skipping</td>
<td>64kbp included from frame 0</td>
<td>Both exons out of frame</td>
<td>Intermediate</td>
</tr>
<tr>
<td>5</td>
<td>Heterozygous c.21196A&gt;G (p.W69X)</td>
<td>Predicted to be null</td>
<td>19kbp included from frame 0</td>
<td>Out-of-frame splice site produced</td>
<td>Intermediate</td>
</tr>
</tbody>
</table>

**Table 2:** Scores of intermediate JEB cases from deep phenotyping. BSA = body surface area affected, this includes blisters, erosions, scabs, healing skin, erythema and atrophic scarring. This is given as a score out of 10. Life threatening illness was scored out of 10. All other categories are scored out of a maximum of 5.
Figure 1: Immunofluorescence using GB3 antibody for laminin-332 in cases with LAMB3 splice site mutations
(a) Case 1, complete lack of immunoreactivity compared with control skin
(b) Case 2, complete lack of immunoreactivity compared with control skin
(c) Case 3, reduced and intermittent staining at the DEJ compared to controls
(d) Case 4, non-blistered skin showing patchy and substantially reduced staining in comparison to control.
(e) Case 4, blistered skin demonstrating almost completely absent staining in comparison to control. The reduction in staining intensity is more marked than the non-blistered skin.
Abstract N°: 2030

A genome-wide association study of hand eczema identifies locus 20q13.33 and reveals genetic overlap with atopic dermatitis.

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Introduction & Objectives:

Hand eczema (HE) often has a multifactorial and complex etiology that can be explained by both exogenous and endogenous factors. Endogenous factors include atopic dermatitis (AD). In addition, twin studies revealed that genetic effects also play a role in developing HE and may only be partially explained by genetic overlap with AD. However, the responsible genetic factors are still unknown.

Our primary aim was to identify and characterize genetic loci associated with HE. Furthermore, we aimed to provide more insight into the genetic overlap between HE and AD.

Materials & Methods:

This cross-sectional study used questionnaire-derived and genotype data from Lifelines, a large population-based cohort and biobank study. We performed a genome-wide association study (GWAS) of HE of up to 19,128 individuals (Ncases=2,879), and a GWAS of AD of up to 18,896 individuals (Ncases=1,706) using generalized mixed models. Covariates age and sex were added in every analysis. Additionally, the GWAS of HE was repeated with AD as a covariate to evaluate if the result is independent of AD. We conducted linkage disequilibrium score regression analyses between HE and AD (independent datasets) to analyse the genetic correlation between both skin diseases.

Results:

We identified multiple genome-wide significant variants at locus 20q13.33 associated with HE, regardless of adjusting for AD. The lead SNP (rs8114049) is an intron variant mapping to RTEL1 and RTEL1-TNFRSF6B genes (p = 2.05 x 10^-11). When we adjusted for AD in the HE GWAS model, several variants remained significant and were previously associated with AD in other AD GWASs. This means locus 20q13.33 is pleiotropic for HE and AD. The region at locus 20q13.33 contains several immune regulation genes (TNFRSF6B, ZGPAT, LIME1) that may play a role in the pathogenesis of both HE and AD. We revealed a strong significant genetic correlation between HE and AD (rg = 0.71 - 0.81, p= 0.014 - 0.017), even when HE was adjusted for AD (rg = 0.69, p = 0.012). The GWAS of AD revealed four variants suggestively associated (p < 5 x 10^-07) with AD at three known loci: 1q21.3 (FLG-AS1, FLG), 5q22.1 (SLC25A46, TSLP), and 11q13.1 (OVOL1).

Conclusion:

This study identified an association between variants at locus 20q13.33 and HE, and revealed a large genetic overlap with AD. Our findings provide novel insights into the pathogenesis and genetic factors of HE.
Figure 1. Manhattan plot of hand eczema cases versus healthy controls. Each dot represents a variant with the genome-wide significant lead variant indicated. The red horizontal line represents the genome-wide significance threshold ($p < 5 \times 10^{-8}$).
Abstract N°: 2329

Ectodermal dysplasias in Denmark: identification and characterization of a nationwide cohort

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Introduction & Objectives:
Ectodermal dysplasias (ED) constitute a group of rare genetic disorders of the skin and skin appendages. Common features of EDs include hypodontia, hypotrichosis, and hypohidrosis. Population-based studies into the epidemiology of ED are lacking. We aimed to utilize Danish health registries to identify and characterize a nationwide cohort of patients with ED allowing population-based investigations of the disease epidemiology.

Materials & Methods:
We searched the Danish National Patient Registry for hospitalizations and outpatient contacts with International Classification of Diseases 10th Revision (ICD-10) diagnosis codes indicative of ED from Jan 1st, 1995 to Aug 25th, 2021. We applied three search algorithms identifying patients with ICD-10 codes for (1) EDs specifically, (2) ≥2 cardinal features, or (3) 1 cardinal feature with ≥2 minor features (only at Aarhus University Hospital). Algorithms 2 and 3 also included records of hypodontia in the Danish Central Dentistry Registry (SCOR). We supplemented the search with patients registered in the Danish RareDis Database (2007–2021), the Danish Database of Genodermatoses (2018-2021), and local genetic databases. One author then reviewed the patient’s medical records for validation and detailed patient characterization. We estimated the minimum birth prevalence for birth cohorts 1995–2011 to ensure a minimum attained age of 10 years for the population at the end of the study period.

Results:
Our database search identified 845 patients suspected of ED, for which 792 (93.7%) medical records were available. Our validation confirmed an ED disorder in 320 cases with an additional 77 possible cases, yielding a combined positive predictive value (PPV) of 50.1% [95% confidence interval (CI): 46.6–53.6]. The PPVs of the three search algorithms were (1) 67.0% (95% confidence interval (CI): 62.7–71.0%), (2) 8.2% (95% CI 4.6–14.3%), and (3) 1.8% (95% CI 0–7.2%), respectively. The estimated minimum birth prevalence for all EDs combined (n=161) was 15 cases per 100,000 live births (95% CI: 12–17 per 100,000 live births). Of 397 validated cases, 245 (61.7%) were females. A molecular genetic diagnosis was available for 242 (61%) patients, including ED4 (n=100), IKBKG (n=55), WNT10A (n=21), TRPS1 (n=18), EDAR (n=10), P63 (n=9), GJB6 (n=9), PORCN (n=7), and other rare genes.

Conclusion:
We used the Danish health registries to identify and characterize a validated nationwide cohort of ED patients. With detailed clinical and molecular data, the cohort provides a unique resource for future ED research. The low PPVs of the search algorithms also emphasize the importance of diagnosis validation. The ED prevalence estimated in our study is lower than previously reported, a possible result of this stringent validation and updated disease definition.
Hereditary Leiomyomatosis and Renal Cell Cancer Syndrome in the French-Canadian Population: a Descriptive Study

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Hereditary Leiomyomatosis and Renal Cell Cancer Syndrome in the French-Canadian Population: a Descriptive Study

Introduction & Objectives: Hereditary leiomyomatosis and renal cell cancer (HLRCC) is a genetic disorder characterized by cutaneous (CL) and uterine leiomyomas (UL), and risk of renal cancer (RCC). It is caused by a germline mutation in the Fumarate Hydratase (FH) gene. Founder FH gene variants are thought to lead to a higher prevalence of HLRCC in the French-Canadians. This study aims to describe the demographic and clinical features of a cohort of HLRCC patients.

Materials & Methods: Patients were recruited prospectively from the genodermatology clinic into Cancer Predisposition Biobank (MP-37-2019-4865). A total body skin exam (TBSE) was performed for all patients by a single dermatologist. Pedigree, detailed history, and genetic testing was obtained by the same geneticist. Health related quality of life (HRQoL) was measured with the Dermatology Life Quality Index (DLQI) questionnaire. This study was designed as a cross sectional study based on the first study visit.

Results: We identified 22 females and 11 males with HLRCC with 5 distinct FH gene variants. The founder variant c.1293del (p.Glu432Lysfs*17) was the most prevalent, found in 12 patients of 7 distinct families. Among the 32 patients who agreed to a TBSE, 91% (n=29/32) had CLs which in 24% (n=7/29) were first diagnosed in our clinic. We found that a pseudo-Darier sign was very helpful to confirm the diagnosis of CL and differentiate from CL mimickers (pseudo-Darier sign was present in 100% of cases). The mean reported age at CL onset was 23.5 years-old (range 11 to 44). Of 3 patients who did not present with CL, 2 were under age 23 and 1 patient (a 37 years-old female) had a complete FH gene deletion. CLs were most commonly localized on the arms (n=21/29), back (n=19/29), thigh (n=9/29), chest (n=8/29), shoulder (n=6/29), and less commonly on the abdomen, legs, breast, neck and buttock. Sensitivity to temperature changes and touch were reported in 38% and 31% of cases respectively. DLQI score was 0 in ⅔ of patients, whereas 33% reported reduced HRQoL with DLQI scores ranging from 1 to 10 (mean = 4). ULs were reported in 50% of female patients, leading to hysterectomy prior to age 40 in 54% of cases. Four female patients (4/22) reported a history of miscarriages associated with ULs.

Conclusion: Our findings highlight the founder variant (c.1293del) as the most common mutation in theFH gene in our French-Canadian HLRCC cohort, which is thought to account for significantly higher prevalence of HLRCC in Quebec compared to worldwide. CL are highly prevalent in HLRCC but an important proportion of adult patients are unaware of their lesions due to their indolent presentation. While HRQoL is unaffected in most patients, almost a third of our patients reported reduced HRQoL due to their CLs. UL are very common among female patients and may lead to gynecological complications.
Abstract N°: 2740

**HyperIgE syndromes, two cases with different clinical presentations**

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**Introduction & Objectives:**

HyperIgE Syndromes belongs to the group of primary immune deficiencies. They are characterized by the triad: ecema, recurrent skin and lung infections and high IgE levels. Diagnosis is based on molecular genetic analysis. We report two cases with different clinical presentations.

**Materials & Methods:**

**Case 1:** a 2-year-old boy from a non-consanguineous marriage was referred for erythemato-squamous, erosive scabby and pustular lesions associated with pruritus and fever. He had multiple similar rash episodes since birth as well as numerous events of pulmonary infections with respiratory distress. Examination revealed disseminated erythematous lesions and large pustules with xerosis. The boy had fever and average general condition. Laboratory tests showed hyperleukocytosis (18,000/mm³) with eosinophilia (4,500/mm³) and anaemia, as well as high IgE levels (2500 IU/l). Skin swabs and bacterial culture identified multi-resistant staphylococcus aureus. Chest CT revealed nonspecific parenchymal lesion probably related to recurrent lung infections. Clinical features and laboratory findings were consistent with HyperIgE syndrome. Genetic analysis could not be performed.

He was treated initially with vancomycin (50 mg/kg/day) leading to mild improvement, then received intravenous immunoglobulin (0.4 g/kg), trimethoprim/sulfamethoxazole (480 mg/bid) and voriconazole (50 mg/d) with a better outcome.

**Case 2:** a 7-year-old boy from a consanguineous marriage with a history of eczematous dermatitis was referred for disseminated molluscum contagiosum. Examination revealed numerous pink umbilicated papulo-nodular lesions disseminated over the entire body including the face. Mild eczematous lesions on the face and diffuse xerosis were noticed. Laboratory testing showed high level of IgE (3200 IU/l). Skin biopsy demonstrated histological characteristics of molluscum contagiosum. Chest CT scan revealed lingular alveolar pneumonia. HyperIgE syndrome was suspected based on clinical and laboratory findings then confirmed by genetic analysis which revealed DOCK8 mutation. The child was treated with intravenous immunoglobulin (0.4g/Kg) in combination with trimethoprim/sulfamethoxazole (480 mg/bid) and voriconazole (50 mg/d) leading to the resolution of half of the lesions.

**Results:**

HyperIgE syndrome comes in two varieties - autosomal dominant (AD) or autosomal recessive (AR) - which are clinically different. The AD form is caused by a mutation in STAT3 is characterized by the classic triad of high serum IgE, recurrent cutaneous and pulmonary infections, and eczema. Our first patient’s features may be consistent with this form. The AR type is caused by mutations in DOCK8 gene and seem have similar clinical presentation with distinguishing features such asthma, food/environmental allergies, recalcitrant, widespread viral infections and malignant neoplasms. Management remains largely supportive, based on prophylactic anti-bacterial and antimycotic agents. Many patients have received benefits from immunoglobulines. Haematopoietic stem cell transplantation has also achieved positive therapeutic effects. Both patients improved by combination of anti-bacterial and anti-mycotic medications, and immunoglobulines.
Conclusion:

Dermatological manifestations of HyperIgE syndrome are early and consistent. The dermatologist has an important role in the early diagnosis and management of this condition.
Prevalence and Predictive Value of Cutaneous Leiomyoma in Screening for Hereditary Leiomyomatosis and Renal Cell Cancer in the French-Canadian Population

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Introduction & objectives: Hereditary leiomyomatosis and renal cell cancer (HLRCC) syndrome predisposes individuals to cutaneous (CL) and uterine leiomyomas (UL) and a 15% life-time risk of aggressive early renal cancer (RCC). HLRCC is caused by a germline mutation in the fumarate hydratase (FH) gene. It is thought to be prevalent in the French-Canadian population due to a founder effect. Available literature suggests that CL’s are present in 71% of HLRCC cases. However, in our practice this is not the case. This study’s objective was to evaluate the prevalence of CLs and the utility of FH staining in a French-Canadian HLRCC cohort.

Materials & Methods: Patients were recruited prospectively from the multidisciplinary genodermatology clinic into Cancer Predisposition Biobank (MP-37-2019-4865). A total body skin exam (TBSE) was performed for all patients by a single dermatologist. Pedigree, detailed history and genetic testing was obtained for patients by the same geneticist. When in doubt, a skin biopsy of CLs was performed to confirm the diagnosis.

Results: In total,** 44 patients were referred for a suspected diagnosis of HLRCC to our clinic between December 2022 and April 2023. Of 44, 30 had CL (68%). Almost all patients with clinically visible CLs (29/30 or 97%) tested positive for FH gene pathogenic variants. The single patient who tested negative had a linear distribution of CLs and was presumed to be mosaic for FH mutation. All of the 14 individuals without CL (32%) underwent genetic testing, and 11 (79%) had no FH gene variant detected and thus were negative for HLRCC. The 3 patients who tested positive for FH gene mutation included 2 patients under the age 23 as well as a 37-year-old patient with a complete FH gene deletion. Skin biopsies were performed in 11 patients (all with pathogenic germlineFH variants) and immunohistochemistry analysis showed: loss of FH staining (n=6/11), weak staining (n=2/11) and retained staining (n=3/11).

Conclusion: TBSE by a dermatologist had a high sensitivity (90.6%) and specificity (91.7%) with a positive predictive value of 96.7% for HLRCC diagnosis. Thus, performing a TBSE in dermatology is a strong tool in assessing the risk of HLRCC. The sensitivity and specificity of TBSE may however vary based on the patient’s age whereas we believe that the absence of CL noted in ⅔ patients carrying pathogenic variants was likely due to the later penetrance of CL. These patients will be followed over time. Importantly, retained FH staining on immunohistochemistry does not rule out a germline pathogenic FH variant as some staining was seen in almost 50% of studied patients. We recommend that all patients with multiple CLs (regardless of the FH immunohistochemistry staining status) undergo clinical assessment for HLRCC and most importantly, lifelong renal cancer screening.
Madelung’s disease and homeless patients: case series and review of literature

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Abstract N°: 2962

Madelung’s disease and homeless patients: case series and review of literature

Introduction & Objectives:

Madelung disease, also known as multiple symmetric lipomatosis or Launois-Bensaude syndrome, is a rare lipid metabolic disorder and it is manifested by a symmetrical accumulation of nonencapsulated adipose tissue deposits, mainly around the head, neck and shoulders.

Fat deposits can grow causing a variety of symptoms, interlalia, dysphagia, breathing difficulties, neck stiffness and headache. Madelung’s disease can occur in all ethnic groups but is usually found in Mediterranean and European populations. Men aged 30–60 years, chronically abusing alcohol are the most commonly affected.

Materials & Methods:

We report two cases of Madelung’s disease in frail and homeless patients.

The first patient, a 45-year-old Romanian man, smoker with arterial hypertension and alcohol dependence syndrome showed prominent masses of adipose tissue on right cheekbone and right submandibular area. The patient presented with a productive cough, therefore he was subjected to quantiferon TB gold which was positive. The remaining physical examination was unremarkable.

The second patient is a 54-year-old Polish man. His history was significant for smoking and heavy alcohol consumption. At physical examination he showed the typical distribution consists of massive lipomatous deposits around the neck, which gives the classic descriptions of “buffalo hump”, also multiple lipomas located on arms, shoulders, trapezius, along back and gynecomastia were noted.

Results:

We report these cases in homeless patients to emphasize the importance of early diagnosis. Patients with Madelung’s disease can develop functional symptoms including dysphagia, odynophagia, or hoarseness as a result of fatty deposits compressing the cervical region. Madelung’s disease is less well known and can go undiagnosed for years.

Conclusion:

It is important to focus on skin health among fragile and vulnerable persons to improve their quality of life and restore their dignity. We need to reduce barriers in accessing health care including skin care. Prevention and treatment, especially for the most vulnerable subjects, should be a priority for the public health and social system.
Papular epidermal nevus with “skyline” basal cell layer: two new cases of siblings

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Introduction & Objectives:

Papular epidermal nevus with “skyline” basal cell layer (PENS) is recent type of epidermal nevus, characterized by keratotic papules or plaques. Dermatological lesions have been described alone or associated with other symptoms as part of a neurocutaneous syndrome. Histology reveals: hyperkeratosis; rectangular acanthosis; and the “skyline sign”, an arrangement of cells with supranuclear cytoplasmic in a palisade along the basement membrane. We describe two siblings with this entity.

Case report

A 19-month-old male patient came to the clinic with a series of skin lesions on the neck, back and arm since birth. Physical examination revealed yellowish hyperkeratotic plaques on the neck, back and arm.

Subsequently, when his little brother was born, he also developed similar localized lesions on left shoulder, left iliac fossa and belly button and neck. Both siblings were in good general health, with no dysmorphic features or extracutaneous anomalies. Histopathologic examination demonstrated a typical “skyline pattern”.

Conclusion:

Six cases of affected families with PENS have been described, of which two are between siblings and the rest from parents to children, a total of 13 cases. The rest of the cases described in the literature are isolated cases without affecting other family members. This entity was first described by Torrelo in 2011 and Tadini reported the first family with PENS. PENS is clinically characterized by single or multiple keratotic papules or plaques with a rough, flat surface and variable shape, appear at birth or shortly thereafter. Cases of PENS syndrome with neurological symptoms such as epilepsy or mental retardation of later onset have been described. Isolated cases without any other associated pathology are probably underdiagnosed, hence the importance of knowing this entity.
Abstract N°: 3267

The enigma of periorificial desquamating lesions in a child

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Key words: Biotin, Biotinidase, Periorificial

Case report

A 4 year old female child born out of third degree consanguineous marriage presented with cutaneous lesions around eyes and mouth along with sparseness of scalp hair for last 2 years. She was born at full term after an uneventful pregnancy by a normal vaginal delivery. The child had a birth weight of 3.2 kg, length of 54 cm and was properly breast fed. There was global developmental delay, gait disturbance along with hearing impairment. There was history of hospitalization for breathlessness 3 months back. There was no history of diarrhoea, seizure or ophthalmological complaints. Family history was unremarkable.

On general examination the patient was afebrile, had an ataxic gait, and was tachypneic with a respiratory rate of 54/minute. The anthropometric measurements were within normal limits for age.

Cutaneous examination revealed periocular and perioral desquamating lesions with secondary impetiginization. Scalp examination revealed diffuse thinning of hair along with widening of central parting and alopecia involving the occiput, however the trichogram was normal. Rest skin, nail and mucosa were uninvolved.

Neurological assessment showed hypotonia along with grade 2 hyper-reflexia and positive bilateral babinski.

Hemogram, liver and renal function tests, random blood sugar, thyroid function test and serum electrolytes were normal. Chest radiograph, electroencephalogram and computed tomography scan of the head revealed no abnormality. Complete ophthalmological examination along with fundoscopy was within normal limits. Arterial blood gas analysis showed high anion gap metabolic acidosis with high serum lactate (45.6mg/dl). The serum levels of biotinidase was found to be as low as 10.5 IU (Normal levels >50 IU). Serum ammonia, serum zinc and sweat chloride levels were found to be normal. Normal levels of amino acids, organic acids and fatty acids were detected on tandem mass spectrometry. Pure tone audiometry revealed bilateral sensorineural hearing loss.

The differential diagnosis for the periorificial lesions included acrodermatitis enteropathica, essential fatty acid deficiency, cystic fibrosis and organic acidurias.

Based on the constellation of above clinical and laboratory findings, a diagnosis of multiple carboxylase deficiency (late onset) secondary to low biotinidase levels, was made.

The patient was started on daily oral supplementation of biotin in the dose of 20 mg/day. On subsequent visit, there was dramatic improvement in the cutaneous lesions along with regrowth of scalp hair and gradual recovery in the gait. However auditory complaints did not show any resolution. Repeat metabolic profile was found to be within normal limits.

Discussion

The clinical features of biotinidase deficiency (BD) include atopic and seborrhoeic dermatitis like eruptions, alopecia, ataxia, hypotonia, developmental delay, sensorineural deafness and immunodeficiency. Most cases with
BD exhibit metabolic abnormalities like ketolactic acidosis, hyperammonaemia, and organic aciduria. Diagnosis of late onset BD is confirmed by measurement of enzyme activity in serum. The present case had an onset of disease at 2 years with perioral and periocular desquamating lesions, alopecia, global developmental delay, ataxic gait, hearing impairment and recurrent chest infections. The patient was started on biotin supplementation with excellent improvement in cutaneous and metabolic disturbances.
Successful combination of isotretinoin and acitretin for the treatment of the disease Galli-Galli

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**Introduction & Objectives:** Galli-Galli disease (GGD) is a rare autosomal dominant genodermatosis, characterized by hyperkeratotic papules and progressive reticular hyperpigmentation involving the neck, trunk, and proximal extremities. GGD falls on a spectrum of reticulate hyperpigmentation disorders, and is thought to be an acantholytic variant of Dowling-Degos disease (DDD). Its mode of inheritance is believed to be autosomal dominant with variable penetrance, but it can occur sporadically, as in our patient. The mechanism of acantholysis in the Galli-Galli variant of DDD remains unknown; however, the authors postulate that this recently discovered defect in keratin 5 and the resulting loss of cell structural stability may be responsible for the epidermal dissolution seen in Galli-Galli disease.

No successful medicinal therapeutic approaches are reported in the literature. Here we describe a case of a severe flare of GGD successfully treated with combination isotretinoin and acitretin.

**Materials & Methods:** Using the PubMed database, we conducted a systematic review of the literature.

**Results:** A previously healthy 52-year-old Caucasian woman presented with a 10-year history of widespread skin lesions. She had recurrent pruritic papular eruptions and slowly progressing brownish lentigo-like macules. The skin lesions began on the trunk and then became generalized, involving the extensor and flexural surfaces of extremities, including the back of the hands, neck, and trunk. Her medical history and medication list were noncontributory. Past treatments included only topical corticosteroids (clobetasol and betamethasone - without improvement. The face, palms, soles, and inguinal area were spared. Histopathologic examination of the skin revealed digitate down-growth of slender, elongated reteridges and thinning of the suprapapillary epidermis. Focal suprabasal acantholysis without dyskeratosis was seen. A superficial, perivascular, predominantly lymphocytic infiltrate with eosinophils was also noted. Despite a variety of potential therapeutic options published in the literature, we decided to try oral isotretinoin with a switch to acitretin. Patient was started on isotretinoin 30 mg daily during 5 months. During treatment with isotretinoin, no new rashes appeared, but minor itching and red persisted. For a good cosmetic result, we decided to stop taking isotretinoin and give acitretin at a dose of 25 mg once a day for another 1 month. Then we reduced the dose to 10 mg per day for 1 month, and the next month every other day 10 mg for another 1 month. Locally, the patient used constant emollients. After at the end of the therapy, peeling and redness completely disappeared, no side effects of retinoid therapy were observed.

**Conclusion:** We would like to inform that combination isotretinoin and acitretin as a promising treatment option for Galli-Galli Disease.
Major histocompatibility complex class I deficiency with important skin lesions and amniotic membrane biological dressing

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Introduction & Objectives:

Major histocompatibility complex class I (MHC I) deficiency is a rare genetic disease caused by severe partial deficiency of the MHC I. Total deficiency is incompatible with life, only patients with low expression of MHC I have the disease. MHC acts in the distinction between self and non-self peptides, providing autoimmune control and defense against intracellular pathogens. These patients do not present opportunistic infections and are more prone to bacterial than viral infections. They are healthy in early childhood, but as they grow, bacterial respiratory tract infections are developed. In the long term, it leads to bronchiectasis, respiratory failure, and death. The most common cutaneous presentation is necrotizing granulomatous lesions, mainly on the face and limbs. This report aims to present a case of MHC I deficiency, considered a challenging diagnosis that required a multimodal treatment approach.

Materials & Methods:

We report a case of a patient with MHC I deficiency with complex diagnosis and treatment.

Results:

A 9-year-old female patient was admitted with a six-year history of ulcers on her nose, malar region, and lower limbs. Her parents were consanguineous. The child was extensively investigated at another hospital and treated for infectious diseases without improvement. The anatomopathological exam revealed chronic granulomatous dermatitis with extensive necrosis in the papillary dermis. Immunophenotyping of blood lymphocytes revealed a deficiency of CD8 T lymphocytes. The flow cytometry confirmed the diagnosis of MHC I deficiency. Before receiving a skin graft, our patient received six medical interventions for her lower limbs wounds, once a week, with amniotic membrane biological dressings from our tissue bank, along with systemic antibiotics. During this period, she had an improvement in the skin lesions, however, she presented a decline after the skin graft was placed. Currently, our patient is under outpatient medical follow-up, with a slow decay in skin lesions, with continuous antibiotic therapy without serious respiratory repercussions.

Conclusion:

The MHC I skin lesions begin with a small pustule or subcutaneous nodule that expands and tends to ulcerate. The healing is slow, leading to scarring and mutilation. The diagnosis is confirmed by flow cytometry and HLA molecular typing. Treatment options are scarce, based on preventing the progression of respiratory failure and skin infections, local care, and antibiotics. The amniotic membrane expresses molecules of the MHC complex and produces several growth factors, angiomodulatory cytokines, antibacterial peptides and a wide range of anti-inflammatory agents, improving wound healing. This report highlights the importance of early and accurate
diagnosis of MHC I deficiency and the challenges in managing this rare genetic disease.
Abstract N°: 3496

Oleogel-S10 for chronic wounds in EB: preliminary result of the real-world experience

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Introduction & Objectives:

Oleogel-S10 contains a birch-extract and is the first approved drug for the treatment of junctional epidermolysis bullosa (JEB) and dystrophic epidermolysis bullosa (DEB) wounds in the EU. The phase III trial included 223 patients and showed an increase of wound healing in recessive DEB (RDEB) patients of 44% as compared to 26.2% in the control group, whereas there was no convincing effect in JEB. To assess the effects of Oleogel-S10 in a real-world setting, we performed an observational study between September 2022 and April 2023.

Materials & Methods:

Eleven consecutive EB patients (6 males and 5 females, mean age 25 years, range 6-55) were included. Three patients had intermediate JEB, two intermediate RDEB and six had severe RDEB. Chronic wounds that did not heal with standard care were chosen for treatment. They were localized on arms, legs, head, neck or on the gluteal region. The wound area was variable, ranging from 1cm² to more than 20cm². Patients were instructed to use Oleogel-S10 on the selected wounds at each dressing change and to take follow-up pictures every two weeks. Wound healing, pain and itch were assessed at each follow-up visit.

Results:

Altogether, data from nine patients were obtained and used for evaluation. In eight of nine patients, faster wound healing and partial wound closure were observed. However, wounds relapsed in four cases, and in two patients worsening of the wound situation occurred during the observation period. Under the therapy, reduced itch was reported by five (mean value of itch score before treatment 6.8 and after 3.0; p=0.0014) and reduced pain by four patients (mean value of pain score before treatment 7.0 and after 3.0; p=0.0049). Other effects were reduction of wound bleeding (in three of nine patients) and of inflammation (in two of nine patients). Notably, all three patients with intermediate JEB benefited from the treatment. They showed faster wound healing leading to partial closure, although the wounds relapsed because of new blisters. Except of one child with intermediate RDEB, all other RDEB patients experienced partial wound closure and faster wound healing. Two patients showed undulating improvement and relapsing of the wounds on same localizations.

Conclusion:

The limitations of the study are the real-world setting, the low number of patients, and the variability of the wounds in respect to size and localization. Although the effect was variable and the course of the wounds undulating, all patients continued using Oleogel-S10.
Abstract N°: 3743

Case Report: The importance of skin cancer screening: Large squamous cell carcinoma in a patient with syndromal ichthyosis

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Introduction & Objectives:

Ichthyoses are among the more rare diseases. With a prevalence of around 1:250 births ichthyosis vulgaris is the most common and best known. They are usually caused by a genetic keratinization disorder, making patients suffer from scaly hyperkeratosis of the skin. Syndromal ichthyoses are a subtype of ichthyoses in which other organ systems are also involved. Keratitis-Ichtyosis-Deafness (KID) syndrome is caused by a mutation of a gene encoding a gap junction protein, (specifically a mutation in the GJB2 gene (13q11-q12) of the gene product Connexin-26). This leads to hearing impairment and ocular involvement with keratitis in addition to generalized erythroderma and severe skin scaling. About 15% of patients also develop squamous cell carcinoma, which is likely a common cause of death due to its poor prognosis in KID syndrome. Current studies are sparse due to the rarity of the disease, so more research is needed on the incidence and prevention of malignancies in congenital and acquired keratinization disorders such as KID-syndrome.

Materials & Methods:

A 52-year-old female patient with KID syndrome diagnosed at birth was admitted to our university hospital. She initially presented with an unclear, 20x5cm large and about 7cm deep gaping, heavily oozing ulceration in the area of the left groin. In addition, erythrokeratoderma was prominent on the face and hands. Multiple brownish-reddish plaques, some of them appearing verrucous, were seen on the feet, as well as scaling on the entire trunk. Other known diagnoses included hearing loss, keratitis of the eyes, and previous psychiatric illnesses. The patient denied having B-symptoms.

Results:

The swab of the ulceration only showed colonization with skin germs. In addition, a punch biopsy was performed, which confirmed the suspected diagnosis of squamous cell carcinoma. Staging examinations further revealed a fused lymph node conglomerate on the left inguinal side, several small lymph node metastases on the left iliac side, and an unclear pulmonary mass. Due to inoperability, we initiated a checkpoint inhibitor therapy with Cemiplimab and additional radiotherapy. Unfortunately, the tumor continued progressing rapidly.

Conclusion:

In clinical practice, ichthyoses are not such a rare clinical picture, with keratitis-ichthyosis-deafness syndrome being a particular subtype of syndromal ichthyoses. So far, only a few case reports of KID syndrome and squamous cell carcinoma have been published. The current hypothesis regarding the origin of the disease favors a combination of chronic inflammation, immunologic factors, and genetic factors, although the ultimate etiology remains the subject of current research. With the publication of this case report we want to point out the importance of regular skin cancer screenings, especially in patients with congenital keratinization disorders, such as ichthyosis.
When the sun cause pain - recurrent edema in a 12-year-old patient

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Introduction & Objectives: Erythropoietic protoporphyria (EPP) is an inherited disorder of porphyrin metabolism caused by decreased activity of ferrochelatase, the final enzyme of the heme biosynthesis pathway that catalyzes iron binding to protoporphyrin IX. Clinically, EPP is characterized by pain and burning of the skin accompanied by erythema and swelling. These symptoms appear in a very short time after exposure to the sun. The incidence of the disease ranges from 1/75 000 to 1/200 000. The diagnosis of erythropoietic protoporphyria is difficult, as usually hereditary angioedema and allergic reactions are considered in the differential diagnosis.

Materials & Methods: A 12-year-old girl was admitted to the dermatology department for diagnosis and treatment of painful swelling and erythema mainly in the face and upper limbs, appearing periodically from the age of 8 years, usually associated with sun exposure. Based on clinical symptoms and history, erythropoietic protoporphyria was suspected. Laboratory tests revealed a positive spectrum of porphyrin fluorescence in plasma (emission 634 nm), protoporphyrin concentration in erythrocytes (6813.4 nmol/l, with normal range up to 130 nmol/l), as well as increased excretion of protoporphyrin in feces (549.1 nmol/g, with range 0-100 nmol/g) and zinc-protoporphyrin in erythrocytes within normal range. The patient and her family underwent genetic testing for mutations in the FECH gene, encoding ferrochelatase.

Results: Based on the clinical picture and laboratory test results, the diagnosis of erythropoietic protoporphyria was confirmed and it was recommended to use strict photoprotection and avoid fluorescent lamps. The patient undergoes regular checkups of laboratory tests and liver ultrasound.

Conclusion: EPP is a rare metabolic disorder. The first clinical manifestations of this disease occur most often in childhood. EPP should be considered in patients with burning sensations and pain, as well as erythema and swelling of the skin, which are disproportionally severe in relation to the exposure to ultraviolet radiation.
Warburg-Cinotti syndrome, a novel case and literature review

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Introduction & Objectives:

Warburg-Cinotti syndrome is a recently described entity characterized by the presence of acroosteolysis, digital flexion contractures, corneal neovascularization, keloid formation, ulcerations, and atrophy of subcutaneous cellular tissue as its main manifestations.

Clinical Case:

A 36-year-old woman was referred to our department back in 1999 for a “complex polymalformative syndrome”. Among other clinical findings, she presented deforming fibromatosis of the feet and distal lower extremities with ulcerations, cicatricial alopecia, blepharophimosis, conjunctival pseudoterigium, bluish sclerae, flexion contractures of the fingers of both hands, winged ears, bulbous nose, recurrent pneumothorax and cholesteatoma. Complementary tests (including karyotype) performed during those first years of follow-up did not allow to identify the syndrome. C-kit was positive on some cutaneous biopsies. In 2007, the progression of fibromatosis on both feet led to impaired mobility. Thus, treatment with Imatinib 400 mg daily was started. The latter slowed down the progression of the process, however, this treatment was discontinued after two years.

Recently, exome sequencing revealed a heterozygous mutation in DDR2 gene (c.1829T>C (p.L610P)), which allowed the confirmation of Warburg-Cinotti syndrome. Despite the reintroduction of imatinib, plantar fibromatosis progresses.

Conclusion:

Herein we present the first case described in Spain of Warburg-Cinotti syndrome. Despite its exceptionality, recognizing its clinical phenotype can be the main key to suspect and diagnose this entity. To date, two variants of this syndrome have been described depending on DDR2 gene mutations. The latter encodes a tyrosine kinase; therefore, it has been postulated that tyrosine kinase inhibitors may be useful for treating this condition.
Abstract N°: 3929

Hypohydrotic ectodermal dysplasia associated to immunodeficiency : About 4 cases.

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Introduction & Objectives:

Hypohidrotic ectodermal dysplasia (HED) is a rare inherited affection caused by impaired development of the ectodermal appendages. It is characterized by a primary defect in at least one of the following tissues: nails, hair, sweat glands, or teeth.

We report four original HED cases associated with immunodeficiency.

Materials & Methods:

Results:

Case 1: A 15-year-old boy, from a first-degree consanguineous marriage, who has since the age of 22 days, multiples episodes of unexplained extended fever and repeated infections leading to several hospitalizations. Clinical examination showed sparse hair, dry skin, a thick lower lip and facial dysmorphia made of broadening the nose’s base, ears detachment and hypertelorism.

Case 2: A boy of 5 years from a non-consanguineous marriage who presents since the age of three months, repeated diarrhea and two pneumonia episodes. HED diagnosis was underlined at the age of one year. Clinical examination showed a pilar dystrophy, dry skin, a thick lower lip and conical teeth.

Case 3: A boy of 16 years, from a non-consanguineous marriage, HED diagnosis was underlined at the age of one month and the disease’s development was typical with repeated Respiratory infection episodes. Clinical examination showed a dry skin, a thick lower lip, conical teeth and hypertelorism.

Case 4: A 14-year-old boy has, since the age of 6 months, repeated respiratory infections treated as outpatient as well as episodes of hyperthermia treated by self-medication. He also presents a pilar dystrophy, rare and conical teeth and facial dysmorphia made of broadening of the nose base, a prominent forehead and hypertelorism. To not that his uncle presents similar symptomatology.

The dosage of immunoglobulin and lymphocyte sub populations was normal for the four patients.

Conclusion:

Hypohidrotic ectodermal dysplasia (HED) is characterized by hypotrichosis (sparseness of scalp and body hair), hypohidrosis (reduced ability to sweat), and hypodontia (congenital absence of teeth). The cardinal features of classic HED become obvious during childhood. The scalp hair is thin, lightly pigmented, and slow growing. Sweating, although present, is greatly deficient, leading to episodes of hyperthermia.

Classic HED can be diagnosed after infancy based on physical features in most affected individuals.

Our cases originality lies in the extreme HED rarity with an incidence of 1/100000 births. The occurrence of repeated and unexplained febrile episodes in infants is an important semiological sign. The underlined vulnerability to infection should suspect immunodeficiency often associated. Indeed, the HED-DI is a form which
combines HED cardinal signs manifestations of immune deficiency. It is due to mutation of genes especially NEMO and rarely IKBα. The most frequently associated infections are respiratory tract, gastrointestinal, head and neck, bone, skin and soft tissues. The immune deficiency type is dominated by hyperIgM syndrome. In our patients, immune deficiency cannot be ruled out despite the normality of immunological tests.

The occurrence of repeated and unexplained febrile episodes in infants with sparse hair, dry skin and facial dysmorphia is an important semiological element. A noted vulnerability to infection should suspect an associated immunodeficiency.
Familial pityriasis rubra pilaris (Atypical juvenile type V): A report of three cases in a single family treated with isotretinoin

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Introduction & Objectives:

Pityriasis rubra pilaris (PRP) is an uncommon dermatosis of unknown etiology. The familial subtype is rare and usually presents as type V PRP. The use of oral retinoids in treating PRP is promising given reports of its success in case reports.

Herein, we report three cases of PRP arising in 3 siblings and highlight a satisfactory response with oral isotretinoin.

Materials & Methods:

We present the case of 3 siblings whose parents are first cousins. The oldest sister is aged 14 year old and the middle sister is 9 year old. The diagnosis of PRP type V was based on the presence of characteristic clinical and histopathological features. Both patients showed well-demarcated erythematous plaques coalescing into large areas interspersed with islands of normal skin, follicular papules, orange palmoplantar keratoderma, and a lack of psoriasis-associated nail changes. They were both treated with acitretin and topical corticosteroids incontinuously during 5 years. Given the unsatisfactory response with acitretin, a treatment with isotretinoin 0,5mg/kg per day was started and both patients showed a marked improvement within 2 months.

Further inquiry into the family history brought out the interesting revelation that a similar type of affection seemed to be plaguing the younger brother aged 10 months old who presented eczematous changes of the skin and ichthyosiform scale on lower extremities. The patient was treated with emollients and topical corticosteroids. The evolution of the disease was largely identical.

Results:

The familial form of PRP is rare and begins typically in early childhood and has a gradual onset. Most of the familial cases are of type V (atypical juvenile type) as it is the case in our report. It is usually present at birth or appears during the first years of life and runs a chronic course. The evolution of juvenile PRP remains unpredictable. It is characterized by prominent follicular hyperkeratosis, diffuse orange palmoplantar keratoderma, and erythema. Patients with the familial subtype can have atypical morphologic findings, such as ichthyosiform features and potential sclerodermatous changes of the hands and feet. However, its occurrence among members of a single family appear to be inherited as autosomal dominant with variable expression and reduced penetrance. Recently, gain-of-function mutations in CARD14, which encodes the caspase recruitment domain family member 14, were identified as a cause of familial PRP.

Given the rarity of this subtype, the management of juvenile PRP is challenging. In the pediatric population, a conservative treatment approach, including topical therapy, is frequently used, whereas systemic treatments are reserved for patients with a severe disease that is refractory to therapy.

Systemic retinoids are considered first-line systemic agents in moderate-to-severe disease with recommended
dosages of 1 mg/kg daily isotretinoin or 0.5 mg/kg daily acitretin with marked improvement in 3 to 6 months. Other therapies include methotrexate, cyclosporine, azathioprine phototherapy and biological immunosuppressants as ustekinumab.

**Conclusion:**

The awareness of familial PRP is important for early and accurate diagnosis and administration of appropriate therapy.
Nevoid Basal cell carcinoma syndrome with secondary osteoma cutis: a case report and literature review

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Introduction & Objectives: Nevoid basal cell carcinoma syndrome (NBCCS) is a rare genetic disorder associated with basal cell carcinomas (BCC), palmar pits, skeletal anomalies, jaw cysts, and central nervous system involvement. Osteoma cutis is a benign condition defined as the eruption of an osseous structure in the skin. Osteoma cutis may be divided into a primary and secondary type and the latter is most often associated with chronic inflammatory diseases that lead to the degradation of collagen fibers, with other causes, including trauma and neoplasms. There are only a small number of case reports and case series of BCC associated with secondary osteoma cutis. We conducted a literature review targeting the secondary osteoma cutis of NBCCS that have not been well characterized.

Materials & Methods: We conducted a literature search from 1960 to 2022 utilizing specific keywords and criteria and excluded non-clinical articles. A total of 2 articles were ultimately used for the literature review.

Results: We describe a case of a 69-year-old Japanese female diagnosed with NBCCS found to have secondary osteoma cutis within several BCCs. She was referred to our University Hospital with multiple tumor lesions of the skin. The lesions started to develop when she was 60 years old and thereafter increased in number. Histology revealed superficial and nodular basal cell carcinomas. Just beneath BCC nests in the lower dermis, several basophilic oval-shaped membranous structures were positive with Kossa stain. A total of 4 basal cell carcinomas were surgically removed and microscopically investigated. Further clinical and imaging examinations confirmed palmar pits and calcification of falx cerebri. The spectrum of pathological findings met the diagnostic criteria of NBCCS.

Conclusion: There are only two case reports of NBCCS associated with secondary osteoma cutis. A hamartomatous process is suggested to explain these conditions. Although the pathogenesis of secondary osteoma cutis in the setting of NBCCS remains to be determined, it has been speculated that growth factors and bone morphogenetic proteins produced from myofibroblasts may be involved in the development of the osteogenesis in primary osteoma cutis. When the histopathologic examination reveals bone formation in the skin, Dermatologists should consider the possible presence of an adjacent malignancy, such as BCC and NBCCS.
Gastrointestinal neuroendocrine tumour as a cause of pruritus in a patient with Neurofibromatosis type 1

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Introduction:
Neurofibromatosis type 1 (NF1) is an autosomal dominant genetic disease that is caused by a mutated NF1 tumour suppressor gene. The incidence varies from 1:3,000 to 1:5,000. Patients are presented with multiple cafe-au-lait macules on the skin, skinfold freckling, Lisch nodules in the eye, and cutaneous neurofibromas. Other organs are also affected (scoliosis, gliomas of the optic nerve in 15% of patients, glioblastoma, tumours of the peripheral nerves, endocrine disorders, and mental disabilities). Mast cells in the tumours can induce severe pruritus in some patients with numerous neurofibromas. Pruritus is a common symptom of biliary obstruction. There have been cases described where obstruction can be caused by tumours in NF1. In these patients, the gastrointestinal tract is mostly affected by pancreatic neuroendocrine tumours, gastrointestinal stromal tumours (GIST), carcinoids, pheochromocytomas, paragangliomas and hyperplasia of the mucosal and myenteric nerves.

Results:
Our patient, a 32-year-old woman, presented with severe pruritus that lasted 3 months. She also reported vomiting after meals and a loss of weight. She was diagnosed with NF1 at the age of 2 years. At the same age, she was treated with chemotherapy for an optic nerve glioma in the right eye. After the treatment, 100% loss of vision in the right eye remained. She has undergone many cutaneous neurofibroma excisions, yet many of the tumours are still visible on her skin. Her height is 140 cm. Her entire skin is pale olive green, with many typical cafe-au-lait macules and axillary and inguinal freckling. When she was admitted to the Clinic of Dermatovenerology for treatment of pruritus, laboratory testing showed that her liver enzymes (AST 147, ALT 201, GGT 1010, and ALP 751) were significantly increased. The serologic workup showed previous infection with the hepatitis B virus (anti-HBc and anti-HBe positive, but HBV PCR negative). Because of the mass found on ultrasound of the abdomen, we performed a CT scan. It revealed an abnormal mass sized 16x15 mm causing obstruction of the ductus choledochus. The patient was referred to the Clinic of hepatology, where an ERCP was performed, a ductal stent was implanted and a biopsy was done. Control liver enzymes after the procedure were normal and pruritus was gone. Histological and immunohistochemical results of bioptic material showed a neuroendocrine tumour of the small intestine grade 2 (NET 2). The patient will be presented to the oncologic team in order to determine further treatment options.

Conclusion:
Pruritus, which can have numerous causes, negatively impacts life quality. In this case, it was one of the signs leading to the diagnosis of a gastrointestinal neuroendocrine tumour. Patients with NF1 may develop tumours with variable histopathological patterns. It is necessary to apply a multidisciplinary approach to their treatment. The aim of this case report is to raise awareness about a variety of symptoms that may indicate complications of NF1.
Introduction & Objectives:

Tuberous sclerosis complex (TSC) is a rare genetic disease characterized by tumor development in the brain, skin, retina, kidney, heart, and lungs. Its clinical manifestation is variable and cutaneous involvement is cardinal for suspecting the diagnosis of TSC. Cutaneous findings develop in an age-dependent manner. In contrast to hypopigmented macules which may serve as the first feature of TSC in early life, angiofibromas and periungual fibromas emerge later in adolescence and adulthood, placing adults with undiagnosed TSC at increased risk for life-threatening TSC-related pulmonary and renal disease. Nearly 20% of patients are diagnosed as adults. We present a case of a woman with cutaneous manifestations who had a diagnostic delay of > 15 years of TS.

Case report

A 45-year-old housewife, presented to our dermatology department with periungual papillomatous and subungual verrucous lesions, which had been progressive in size and number in the last decade. They had been previously treated as refractory warts using cryotherapy without noticeable improvement. Her medical history included surgical treatment of uterine leiomyomas. There was a positive family history of similar periungual lesions of her grandfather. She reported that her 4-year-old son has epilepsy. The clinical examination has shown firm papules with smooth surfaces, skin-colored, varied sizes in 6 fingers and 7 toes. Their implantation was in the lateral and proximal fold. A subungual hyperkeratotic lesion on the thumb of the left hand was seen. Some nail plates showed longitudinal lines and canalicular depressions of variable extension, with some thin whitish ridges. We observed flat, normochromic, isolated, and coalescent papules on the face, suggesting angiofibroma. A biopsy from a periungual papulomatous lesion revealed periungual fibroma. We suspected the case as TS based on the above findings which fulfilled 3 major and 1 minor diagnostic criteria. Routine hematological and urine investigations were within normal limits We recommended a CT scan of the abdomen and chest, and an MR of the brain to evaluate disease manifestation. The patient chose to genetic testing, due to fear of genetic disease involving her son. She genetically tested with TSC1 mutation and was lost to follow-up

Conclusion:

Diagnosis of TSC is based on the presence of at least 2 major or 1 major and 2 minor or more diagnostic features. Delaying in the diagnosis may be because of insufficient criteria for diagnosis until adulthood. Our patient reported minimal morbidity in childhood, cutaneous manifestation in her 30s, uterine leiomyomas at 42 years old, and was diagnosed with TSC in her 45s. Patients with adult-onset disease are less likely to present with seizures, and more likely to present with LAM or angiomyolipomas or TSC-associated skin lesions at the time of TSC diagnosis than those with TSC diagnosed in childhood. The uterine leiomyoma in our patient is in association with TSC. Possible explanations for delayed penetrance include mutations associated with a mild phenotype, mosaicism, and effects of modifier genes.

Once TSC is diagnosed a management and surveillance plan should be implemented. It is recommended to have periodic CT on the chest, brain, and kidneys, also evaluation of other organs indicated by symptoms.
We emphasize regularly monitoring for new organ involvement before meeting the clinical criteria for TSC, because early intervention may reduce morbidity and mortality.
Abstract N°: 4203

Long-term surgical outcomes of superficial radiofrequency ablation of recalcitrant Hailey-Hailey disease affecting the groin

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Introduction & Objectives: Hailey-Hailey disease is a rare genodermatosis characterized by painful eroded plaques with fissuring in the flexures. Although medical management, including newer drugs like naltrexone, provides only modest improvement and frequent flares, superficial radiofrequency ablation has shown promise in removing the affected epidermis, resulting in superficial scarring and preventing further disease flares. Therefore, we aimed to evaluate the long-term outcomes of superficial radiofrequency ablation for recalcitrant Hailey-Hailey disease affecting the groin area.

Materials & Methods: We retrospectively analysed ten cases of Hailey-Hailey disease who had undergone serial sessions of superficial radiofrequency ablation for the lesions involving the groin. All of them had been refractory to medical management. The assessment encompassed physician and patient-reported improvements at 6-month follow-up, evaluation of post-operative downtime and discomfort using a Likert scale (ranging from 0 to 10), and determination of the likelihood of patients recommending the procedure to acquaintances or family members.

Results: In total, 20 flexural areas (bilateral) were subjected to superficial radiofrequency ablation in the ten patients. The mean physician-reported improvement at the 6-month follow-up was 75.2%, while the patient-reported improvement reached 82.4%. Only one out of the ten patients experienced a mild flare-up, which was effectively managed with topical steroids. The average duration of post-operative downtime was 10.4 days, and 60% of patients reported a discomfort score of 7 immediately after the procedure. Remarkably, all patients expressed strong advocacy for the procedure, recommending it to others afflicted with the same condition.

Conclusion: Superficial radiofrequency ablation is a simple and effective treatment modality for a debilitating disease like Hailey-Hailey with long-term clinical remission.
Abstract N°: 4205

NLRP12 and IL36RN mutations in a Portuguese woman with autoinflammatory syndrome

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Introduction & Objectives:

Autoinflammatory diseases (AID) are a genetically heterogeneous group of diseases driven by abnormal activation of the innate immune system. Patients share recurrent flares of fever, elevation of acute phase reactants, and variable clinical manifestations, including a wide range of cutaneous lesions.

Familial cold urticaria syndrome-2 (FCAS-2), caused by NLRP12 mutations, belongs to the group of cryopyrin-associated periodic syndrome and is characterized by urticarial skin lesions, while patients with deficiency of IL-36-receptor antagonist (DITRA) have mutations in IL36RN, and typically present with generalized pustular psoriasis (GPP).

Materials & Methods:

We report the case of a woman with autoinflammatory syndrome who was found to harbor simultaneously mutations in the NLRP12 and IL36RN genes.

Results:

A 35-year-old Portuguese woman with recurrent symmetrical inflammatory polyarthralgia since the age of 30, was admitted to our Dermatology Department with a one-week dermatosis consisting of painful well-delimited erythematous papules and plaques on the nose, ears, forearms, hands, legs, and feet, along with fever, worsening of polyarthralgia, and malaise. A generalized sterile pustular eruption affecting 60% of the body surface developed six days later after admission.

She reported a similar milder episode, characterized by erythema and desquamation predominantly on the extremities, accompanied by fever, which was presumptively diagnosed as vasculitis and treated with oral steroids.

Laboratory tests showed leukocytosis with neutrophilia and elevated C-reactive, while serological markers for systemic autoimmune, cryoglobulin, and complement levels were within normal limits. Skin biopsies revealed a combination of a pustular psoriasis-pattern and a neutrophilic urticarial dermatosis-pattern. Genetic analysis for AID identified two heterozygous missense mutations of the NLRP12 gene and one heterozygous variant of the IL36RN gene.

The diagnosis of FCAS-2, with superimposed GPP in association with IL36RN heterozygous mutation, was established. Treatment with prednisolone 20mg/day with gradual taper resulted in a good clinical response, and the patient remained asymptomatic with a maintenance dose of 5 mg/day.

Conclusion:

In this patient, who presented with painful acral erythematous dermatitis, followed by a generalized pustular eruption, we hypothesize that the full-blown phenotype derives from the coexistence of mutations of both
NLRP12 and IL36RN genes, likely having an additive effect on neutrophilic inflammation.

This report highlights the importance of genetic screening for AID in patients with unexplained periodic fever syndromes, to avoid misdiagnosis and improper treatment. Further research is required to clarify the genotype-phenotype correlation in these diseases.
Abstract N°: 4230

**Early-onset recurrent panniculitis as a phenotype of NLRC4-associated autoinflammatory syndrome: Characterization of pathogenicity of the p.Ser445Pro NLRC4 variant**

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**Introduction & Objectives:**

Autoinflammatory diseases (AID) are inborn errors of immunity characterized by episodes of sterile inflammation in the absence of infection or autoimmunity. The group of inflammasomopathies includes those AID caused by variants in the constitutive proteins of the inflammasome (i.e. NLRP3, NLRC4) or in their regulatory proteins. Dominantly inherited NLRC4 gain-of-function (GoF) variants cause an inflammasomopathy with diverse clinical forms ranging from infantile enterocolitis (AIFEC) to familial-cold autoinflammatory syndrome (FCAS4). FCAS4 represents the milder phenotype and is characterized by recurrent episodes of fever, arthralgias and a cold-induced urticarial-like rash from childhood. Characteristically, NLRC4 GoF variants lead to NLRC4-inflammasome overactivation and increased IL-18 production.

The objective of this study was to describe the clinical and histological findings observed in a family with early-onset, recurrent episodes of fever and panniculitis in which the diagnosis of the inflammasomopathy NLRC4-associated AID (NLRC4-AID) was genetically confirmed. Secondary objectives included the pathogenic characterization of the detected variant, and the review of early-onset panniculitis as a potential manifestation of AID.

**Materials & Methods:**

A Spanish family with multiple affected individuals across six consecutive generations was identified. Five individuals (3 affected; 2 unaffected) were enrolled. The patients’ clinical and laboratory data were collected from their medical charts and during consultations. Genetic and functional studies were performed.

**Results:**

The p.Ser445Pro NLRC4 variant found in the 3 affected member was previously described only in a Dutch family. Affected individuals displayed a clinical picture similar to those of the Dutch family, with certain differences: absence of ocular or gastrointestinal symptoms; no relation with cold temperatures; and early-onset panniculitis. Histopathological findings were similar to those previously described in the Dutch family, showing septal and lobular panniculitis with lymphocytic–histiocytic infiltrates, without neutrophils or vasculitis.

Functional analyses performed revealed that the p.Ser445Pro NLRC4 variant led to a basal constitutive activation of NLRC4-inflammasome and increased production of IL-18. These results are of particular interest regarding therapeutic approaches.

**Conclusion:**

We identified a novel pedigree with the p.Ser445Pro NLRC4 variant resulting in recurrent fever and early-onset panniculitis. Functional analyses supported the conclusion that the p-Ser445Pro NLRC4 variant induces a basal
constitutive activation of NLRC4-inflammasome and increased IL-18 production. Prompt recognition of early-onset panniculitis, using disease biomarkers, pathological studies, and/or genetic analysis will allow its early diagnosis, and the administration of targeted therapies.
Abstract N°: 4266

Acute pyelonephritis revealing an acral skin peeling syndrome (APSS)

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Introduction & Objectives:
Peeling skin syndrome (PSS) is a rare autosomal recessive cornification disorder that starts either at birth or later in childhood. It is characterized by continuous shedding of stratum corneum. Two forms of PSS are recognized, namely, Acral PSS (APSS) which is caused by mutations in the TGM5 gene, encoding transglutaminase 5, and generalized PSS.

Acral skin peeling syndrome (APSS) is characterized by a superficial, painless peeling and blistering of the hands and feet skin, without mucosal fragility, worsened by heat exposure, humidity and other forms of moisture, and friction.

We report a case of APSS aggravated and discovered during an acute pyelonephritis attack

Case report:
A 9-year-old boy, with cosanguineous parents, presented to emergency with flank pain, vomiting and high (40 degrees or higher) spiking fever. Laboratory and ultrasonography findings concluded to an acute pyelonephritis. 2 days later the daily clinical examination revealed a superficial painless flaking, more severe and thicker on the soles than palms, which quickly gave way to healthy skin. There was no keratotic papules, and no history of aquagenic aggravation. General and systemic examination revealed no other abnormality. Routine hemogram and urine analysis were tending to normalize. When questioning the patient, he reported since childhood episodes of limited scaling on the palms and heels occurring in the hot periods of summer. Family history was present, two brothers had the same symptomatology which had not been labelled until then.

Skin biopsy showed separation of stratum corneum from stratum granulosum. A diagnosis of APSS aggravated by high fever and swealing episode was retained.

Treatment was symptomatic, with emollients, urea, and measures aimed at reducing maceration and trauma. After 2 weeks, patient was relieved symptomatically. A genetic study was proposed to the patient and his family members.

Discussion:
Peeling skin syndrome is an extremely rare inherited skin disorder characterized by continual, spontaneous skin peeling (exfoliation). The generalized form of PSS is classified into 3 types, A, B, and C, according to the classification system of Traupe and Mevorah. APSS is considered a subtype of peeling limited to the dorsa of the hands and the feet.

Molecular studies among family members with APSS showed homozygous missense mutation in Transglutaminase 5 (TGM5) responsible of a split in a region between the granular layer and the stratum corneum.

The symptoms of APSS are aggravated by hot temperatures, high swealing, humidity and friction.
No effective treatment is reported till date. However, some improvement is seen with keratolytic agents and urea. Topical calcipotriol is also found to be little effective. Other treatment modalities such as topical tar, emollient, topical steroid, methotrexate, and phototherapy had been used but were not effective.

**Conclusion:**

Despite the benign nature of this pathology, it can strongly alter the quality of life, hence the importance of prevention by avoiding traumas and skin maceration in involved regions.
Therapeutic dimensions of Hailey-Hailey disease

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Introduction & Objectives:
Hailey-Hailey disease (HHD or benign familial chronic pemphigus, OMIM 1696000) is a rare acantholytic genodermatosis. HHD is characterized by autosomal dominant inheritance caused by mutations in the ATP2C1 gene resulting in loss of adhesion between epidermal keratinocytes. It typically manifests with painful blisters, erosions, and scaly erythematous plaques, classically involving the skin folds or flexural areas such as the axillae, submammary area, groin, and the perineum, often in a symmetrical distribution. HHD is characterized by remissions and multiple recurrences. Superinfection is frequent and HHD may have an immense impact on patient’s quality of life. Therapy is often challenging due to the chronic relapsing course of the disease and the lack of randomized controlled studies. Therapeutic options include topical antiseptics, corticosteroids, calcineurin inhibitors, local botulinum toxin injections, systemic antimicrobials, retinoids, low-dose naltrexone, immunosuppressive drugs, and biologic agent dupilumab. Interventional therapies such as CO2 or erbium/YAG lasers dermabrasion may also have a good effect.

Here we present three cases of HHD effectively treated with different alternative therapeutic agents.

Materials & Methods:
We report the cases of 3 HHD patients (2 females and 1 male, mean age of 52 years) whose diagnoses were verified by clinical, histological, and molecular genetic diagnostic methods. In all cases, the effectiveness of several local and systemic therapies was limited and severe relapses were frequent. In case one, a CO2 laser dermabrasion technique has been applied. In case two, oral PDE4 inhibitor apremilast was combined with CO2 laser treatment. In case three, a systemic vitamin A derivative alitretinoin was administered.

Results:
In case one, after CO2 laser treatments in different sites, lesions markedly improved (1-year follow-up). In case two, significant improvement was also observed (followed up for 6 months), and in case three, minimal relapses were observed in a 1-year follow-up period.

Conclusion:
Regarding the possibilities of treating HHD, several options are available. Patience and perseverance are the cornerstones of treatment, different patients may have different outcomes and combining or switching therapy is often necessary. In our cases, systemic alitretinoin, apremilast, and CO2 laser dermabrasion effectively controlled relapses. Precision medicine is expected to be successfully applied in the near future as a treatment strategy for patients with HHD.
Abstract N°: 4348

Employing Various Laser Modalities to Improve Aesthetics & Functionality in Genodermatoses' Patients - An Example of a Fruitful Collaboration Between a Genodermatoses Centre of Reference & a University Laser Centre, and Review of the Literature

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Introduction & Objectives:

Patients with genodermatoses who face socio-professional repercussions & discomfort due to major functional and/or aesthetic concerns are increasingly requesting laser treatment due to their effectiveness. Lasers are considered a safe, more precise & minimally invasive procedure options for various genodermatoses that can be physically disfiguring & psychologically distressing. Nevertheless, as genodermatoses are rare, there is scarcity of evidence found in the literature. Therefore, experts usually select lasers based on their clinical judgment & knowledge.

Materials & Methods:

We have retrospectively reviewed & listed a myriad of genodermatoses that were clinically encountered at our national centre of reference along with their respective cutaneous lesions. We then listed parallelly the various laser modalities employed to treat these cutaneous manifestations at our university laser centre between 01/2020 and 04/2023.

Finally, we compared our choice of techniques with those suggested by the currently published case reports and/or case series in the evidence-based literature.

Results:

Lasers employed at our university centre included 10,600 nm CO2 laser (scanned continuous wave & fractional ablative), Q-switch, 595-585 nm Pulsed Dye, 2,940 nm Er-YAG laser (ablative & fractional ablative) in addition to other laser platforms used either alone or in combination. Such treatment modalities have offered an effective therapeutic option both cosmetically and symptomatically to a number of our patients with genodermatoses.

Preliminary results revealed thirty genodermatoses patients treated with multiple lasers mainly ablative CO2 and an overall mean age of 37 years. Our techniques of choice corresponded with those found in the literature as listed in the table below:
Conclusion:

Laser therapy should be considered as an important option for patients with such conditions to improve cosmetics, psychological state, possible social repercussions faced, and overall quality of life. Depending on size, number & location of lesion(s), several passes and multiple sessions might be required. Despite specialized lasers’ excellent safety record and clinical effectiveness, the presence of pain remains the main obstacle to tackle. Patients with genodermatoses usually have recurring cutaneous lesions that are mostly multiple, evolving in nature and commonly located on the face. Pain is therefore inevitable. Consequently, ideal laser treatment might require the use of general anesthesia, locoregional anesthesia, as well as targeted intravenous sedation to improve on patients’ experience.
Case Presentation of Melanoma in a Patient with von Recklinghausen’s (Neurofibromatosis Type 1) Disease

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Introduction & Objectives:

We describe an unusual occurrence of two primary malignant melanomas in a gentleman with neurofibromatosis (von Recklinghausen’s disease; NF type 1). Neurofibromatosis, like malignant melanoma, is believed to be a disorder of neural crest origin, and is associated with a number of different malignancies, but a definite association between cutaneous malignant melanoma and neurofibromatosis has not been established. This case presented as two de novo lesions on the patient’s back, distinct from neurofibromas. The malignant melanoma was not related to a café-au-lait patch or congenital naevus.

Materials & Methods:

The Patient has two primary lesions; with Breslow thickness of 0.5mm and 0.6mm respectively, superficial spreading, pT1a primary tumour lesions treated with wide local excisions. Although these two conditions appear to be unrelated, recent studies have suggested a link between neurofibromatosis and melanoma. There is a lack of literature on the link between patients with neurofibromatosis associated with cutaneous malignant melanoma.

Results:

Although these two conditions appear to be unrelated, recent studies have suggested a link between neurofibromatosis and melanoma.

Conclusion:

There is a lack of literature on the link between patients with neurofibromatosis associated with cutaneous malignant melanoma.
Abstract N°: 4533

Darier’s disease: distinctive clinical features in skin of color.

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Introduction:

Darier’s disease (DD) is an autosomal dominant genodermatosis, with complete penetrance and variable expressivity. Insufficient function of the 2b isoform of the sarco/endoplasmic reticulum Ca²⁺ ATPase (SERCA2b) leads to abnormal intracellular Ca²⁺ signaling. The result is a loss of suprabasilar cell adhesion and an induction of apoptosis.

Its clinical spectrum is wide, and it has been poorly described in V-VI Fitzpatrick skin phototypes. We describe here three cases of Darier’s disease in African patients seen during our dermatological campaign in Malawi in 2022 and 2023. Two of them presented a distinct clinical sign which is typical of darker skin types: guttate leukoderma.

Clinical cases:

Case 1: A 26-year-old woman with no relevant medical history, presented with few years evolution mildly pruritic eruption on the head and trunk. On physical examination we found multiple flat-topped confluent papules, with greasy appearance, on the front, cheeks, and temporal regions. She also had small keratotic papules disseminated on the trunk and limbs. Her baby who came with her, also had similar lesions on the head.

Case 2: A 22-year-old woman with no relevant medical history, presented with few years evolution mildly pruritic eruption on the head and trunk very similar to the previous patient. She also had multiple hypopigmented papules on the trunk and dystrophic nails with subungual hyperkeratosis and V-shaped notches.

Case 3: A 58-year-old man with no relevant medical history presented with a long-lasting mildly pruritic eruption that waxed and waned, on the head and trunk. We could observe similar flat-topped coalescent papules on the temporal region with greasy appearance, keratotic papules that converged in the epigastric region in a Blaschkoid distribution and other similar papules that were disseminated in the rest of the trunk and arms. He also had multiple hypopigmented macules and papules on the upper trunk.

Biopsies of the keratotic papules were performed in all of them with similar findings: suprabasilar cleft formation (acantholysis) and dyskeratotic cells; acantholytic enlarged keratinocytes with pyknotic nuclei surrounded by a clear cytoplasm (“corps ronds”).

Discussion:

Guttate leukoderma was first described by Goodall and Richmond in 1965. It consists of confetti-like...
hypopigmented macules associated with DD. Fewer than 30 cases of DD with GL have been reported in the literature and mostly in patients with higher skin phototype.

Lesions of GL typically appear simultaneously or, more commonly, years before the development of papular lesions. The pathogenesis of GL has not yet been fully elucidated. Several features support GL as a manifestation of the disease itself, rather than secondary postinflammatory change. Histologically, decrease in the density of basal epidermal melanocytes, with variable dyskeratosis and acantholysis can be found.

**Conclusion:**

Given the rarity of GL in DD, dermatologists might be unaware of this unique clinical feature. However, it is helpful to recognize this manifestation: GL often precedes the onset of keratotic papules, thereby serving as an early marker of DD. This finding might also be useful in dark-skinned patients without classic keratotic papules in a seborrheic distribution.
A phase I/II trial on the use of losartan to treat children with recessive dystrophic epidermolysis bullosa

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Introduction & Objectives: Recessive dystrophic epidermolysis bullosa (RDEB) is an inherited skin fragility disorder characterized by lifelong mechanically induced skin blistering, fibrosis-driven pseudosyndactyly, and multi-organ involvement. The fibrosis results in substantially reduced organ function and diminished quality of life. Excessive inflammation and TGFβ activity are implicated in advanced fibrosis in RDEB. There has been significant progress in developing potential treatments for RDEB. Although providing exciting progress in how we can treat RDEB patients, those studies have highlighted concerns about durability and/or safety of the treatments, as well as being rather expensive and laborious. Thus, there is a major need for safe, widely available, systemic treatment options. Preclinical studies have suggested mitigated progression by angiotensin II blockade through losartan.

Materials & Methods: Following highly promising preclinical data in an RDEB mouse model, we initiated the REFLECT open-label, phase I/II trial. Specifically, we evaluated safety and the clinical response to systemic losartan in RDEB. A total of 29 children with RDEB (median age 6 years; range 2 to 14 years) were enrolled, comprising the largest trial with a systemically applied treatment for patients with RDEB. They received oral losartan once daily for a total of 9 months, then tapered for 4 weeks, followed by 3 months follow-up without losartan. EB-specific scores were evaluated and other clinical outcome parameters (pain, quality of life, itch, dysphagia, hand function) were evaluated at five clinical visits. We also analyzed markers for inflammation and fibrosis in sera and skin biopsies.

Results: In total, 29 children were enrolled. Losartan was well tolerated and no treatment-related severe complications leading to a serious safety concern occurred. The patients showed improvement in the RDEB clinical scores EBDASI and BEBS, while the Children’s Dermatology Life Quality Index rose significantly. We also observed a clinically meaningful improvement in weight and height, compared to a natural history control group, as well as in the functional outcome of finger span.

Conclusion: Losartan was well tolerated by children with RDEB, and resulted in a lower disease burden. Our trial data highlight that systemic losartan prevents disease progression, reduces inflammation, and improves the clinical picture. Although it is not a curative treatment for RDEB, it promises substantial benefits as a disease-modifying, systemic treatment, which has in combination the potential to enhance the efficacy of topical gene therapies. Importantly, by showing efficacy of losartan in RDEB in a large cohort of children, we highlight that repurposing of this worldwide available drug could be an efficient and cost-effective treatment for individuals with...
the highly debilitating disease RDEB, even in low-income countries.
A child with LMNA-NTRK1 rearranged spindle cell neoplasm

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Introduction & Objectives:

A subset of mesenchymal neoplasms with NTRK /Neurotrophic Tyrosine Receptor Kinase/ gene fusions represents locally aggressive neoplasms, typically occurring in subcutaneous tissue, with a characteristic immunophenotype (CD34+, S100+) and recurrent kinase gene fusions, most commonly the LMNA /LaMiN A/-NTRK1 fusion. The differential diagnosis includes fibroblastic tumors such as lipofibromatosis and dermatofibrosarcoma protuberans.

Materials & Methods:

We present an 11-month-old girl with a slow-growing erythematous plaque with central atrophy, measuring 1x1.5 cm, on the scalp, which appeared a few months after birth. The parents denied the presence of any change at birth, as well as previous trauma. Lymph nodes were not enlarged. There were no other skin lesions and the child was otherwise completely healthy.

Results:

Routine laboratory analyses were normal. Scalp ultrasonography showed hypoechogenic subcutaneous plaque. Punch biopsy showed neoplastic proliferation consisting of elongated spindle cells, strongly CD34+, corresponding to plaque-like CD34+ dermal fibroma. A complete surgical excision was performed. Morphological, immunohistochemical and molecular analyses excluded dermatofibrosarcoma protuberans; the sarcoma fusion analysis by Next Generation Sequencing test, based on anchored multiplex PCR, demonstrated the presence of LMNA-NTRK1 gene fusion.

Conclusion:

All the findings confirmed the diagnosis of LMNA-NTRK1 rearranged spindle cell neoplasm, a recently described and rare molecularly-defined soft tissue tumor that may have a wide spectrum of morphologies and histological grades, with frequent co-expression of CD34 and S100. Due to the highly infiltrative growth pattern, the tumor has a propensity for local recurrence, if incompletely excised, but none has been shown to metastasize. In our patient, there was no recurrence more than 3 years after the excision. LMNA-NTRK1 fusion serves both as a diagnostic and therapeutic biomarker. Cases with advanced disease may be treated using tyrosine kinase inhibitors.
Bier spots with unilateral mottling in an adolescent

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Universidade Prof. Edson Antônio Velano - UNIFENAS, Dermatology, Alfenas - MG, Brazil; Centro Universitário das Faculdades Associadas de Ensino - UNIFAE, Dermatology, São João da Boa Vista - SP, Brazil

Introduction & Objectives: Elemental alterations of Bier spots are characterized by irregular, whitish spots on the epidermis, surrounded by an erythematous halo, predominantly in the upper limbs, compared to the lower limbs and trunk, asymptomatic, generally self-limited, not requiring specific treatment. Caused by a benign vascular anomaly, it causes physiological vasoconstriction of small vessels, vascular congestion, especially when the limb is lowered or compressed.

Results: A 14-year-old male patient presented white spots on the right upper limb, with an evolution of 8 months. Dermatological examination reveals small hypochromic spots, approximately 1 cm in diameter, with central petechiae affecting only the right upper limb, arm, forearm and back of the hand. When the upper limb is elevated for a few minutes, the lesions disappear. As it can often be a compressive chest injury, a computed tomography scan of the chest was performed to exclude it, which did not reveal any changes. Based on the clinical history and test results, a diagnosis of Bier spots was made, spontaneous spots that in most cases do not have a specific cause. The diagnosis is based on the clinical manifestations and the disappearance of hypochromic lesions in the ascension of the affected limb and diascopy. It is also possible to observe that the lesions enhance when a tourniquet is used around the affected limb and disappear after its removal, corroborating the diagnosis. It does not require treatment and clients should be reassured about the benign and self-limited pathophysiology of the clinical picture.

Conclusion: Small hypochromic spots that are difficult to diagnose due to the restricted clinical presentation in the upper limbs and disappear when the arms are raised. The importance of correct diagnosis to rule out possible malignant causes such as chest tumor.
Abstract N°: 4792

**Progressive Symmetrical Erythrokeratoderma as a differential diagnosis to psoriasis**

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**Introduction & Objectives:**

Psoriasis has varied dermatological manifestations and challenging differential diagnoses. Among them, Progressive Symmetrical Erythrokeratoderma (PSEK) stands out, which will be discussed subsequently.

**Materials & Methods:**

It is reported the case of a 23-year-old female patient who, since the age of 10, was diagnosed with psoriasis. Upon arrival, the possibility of PSEK was suggested due to the set of clinical findings and unresponsiveness to previous treatments.

A direct mycological examination was performed to rule out the presence of dermatophytosis, with a negative result, and two biopsies were collected. Beyond that, a search in literature was made in order to distinguish the diseases.

**Results:**

PSEK is a rare heterogeneous genodermatosis of autosomal dominant inheritance with incomplete penetrance and variable expressivity. The pathophysiology is related to mutations in the genetic coding of the cornified cell envelope (loricrin), in addition to the involvement of the KDSR gene, and has the component of exacerbated proliferation of keratinocytes and dysfunctional differentiation. Lesions are symmetrically distributed, non-migratory keratotic plaques on an erythematous orange or brownish base. It predominates on the extensor surfaces of the knees, elbows, hands, feet, on the face, and 50% of patients have palmoplantar hyperkeratosis. It progresses during childhood and tends to stabilize during adolescence.

Based on literature review, the main points that must be taken into account to differentiate these two entities are:

<table>
<thead>
<tr>
<th></th>
<th>PSEK</th>
<th>Psoriasis</th>
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<tbody>
<tr>
<td>Presence of palmoplantar hyperkeratosis</td>
<td>50%</td>
<td>12%</td>
</tr>
<tr>
<td>Affected areas</td>
<td>Extension areas and extremities</td>
<td>Trunk and sites of trauma (Koebner phenomenon)</td>
</tr>
<tr>
<td>Age</td>
<td>Begins in childhood, stabilizes in adolescence</td>
<td>30 to 50 years-old</td>
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|Histopathology| Orthokeratotic hyperkeratosis;|
|             | Focal parakeratosis; |
Normal or prominent granular layer;
Mild or moderate acanthosis;
Perivascular lymphocytic infiltration in the papillary dermis

Acanthosis with downward elongation of rete ridges;
Thinned or absent granular layer;
Elongated and dilated capillaries;
Suprapapillary thinning;
Inflammatory infiltrate of T cells in the dermis and epidermis

Biopsies performed in this case showed laminar hyperkeratosis, acanthosis, papillomatosis, irregular granular layer and perivascular lymphomononuclear infiltrate. This result, among clinical presentation and evolution of the condition, confirmed the diagnosis of PSEK.

The reported treatments include topical corticosteroids or calcipotriol and systemic retinoids. An improvement of the lesions is expected during the use of medications, with recurrence after interruption.

**Conclusion:**

Progressive Symmetrical Erythrokeratoderma is an important differential diagnosis in suspected cases of psoriasis, and should be considered for patients with clinically suggestive lesions, onset during childhood or adolescence, and poor response to the usual treatments for psoriasis.
Novel recessive loss-of-function mutations in Desmoplakin underlying skin blistering, keratoderma and woolly hair

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Introduction & Objectives:
Desmoplakin is the main plaque protein of desmosomes, which is important in the attachment of the intermediate filaments to the desmosomes and in intercellular adhesion. More than 120 dominant and recessive mutations in the desmoplakin gene (DSP) have been reported. Associated clinical features are keratoderma, blisters, nail dystrophy, woolly hair, cardiomyopathy. We report a case of desmoplakin deficiency with woolly hair, palmoplantar keratoderma and skin fragility in a Caucasian boy.

Materials & Methods:
Physical examination, immunohistochemistry of a skin biopsy, blood sampling and targeted next-generation sequencing (NGS) using a custom panel of genes involved in genodermatoses were performed for diagnostic purpose.

Results:
A fifteen-year-old Caucasian boy presented with a history of skin fragility, blistering of palms and soles since infancy. He was diagnosed with EBS. He was the second child of unrelated, healthy parents. No other relatives were affected.

Physical examination revealed palmoplantar linear hyperkeratotic lesions, thickened and greyish fingernails, dry, fragile, woolly hair which was not seen among his parents nor relatives.

Hematoxylin eosin staining of a skin biopsy of the sole showed enlarged intercellular spaces in basal and suprabasal epidermal cells. NGS of genes involved in genodermatoses revealed a c.8193C>G (p.Tyr2731*) and a c.8321delT (p.Leu2774Argfs*8) variant at the heterozygous state in exon 24 in DSP. These changes were not reported in the HGMD pro database and are predicted to be damaging based on their nature: the first variant leads to a nonsense mutation, the second causes a frameshift producing a premature stop codon. Both are located in the very last exon of DSP and predict truncation of the tail domain of the protein, responsible for the binding of intermediate filaments. Each mutation was inherited from one of the healthy parents. Consistent with these results, immunohistochemistry of a skin section showed a drastic reduction of DSP membranous labelling in basal and suprabasal epidermal layers.

Cardiovascular investigations (ECG, Holter monitoring, echocardiography) were normal. The parents and the patient were informed on the importance of complete cardiac evaluation at least once a year.

Conclusion:
We report two new bi-allelic mutations in DSP which establish the diagnosis of desmosomal disease due to desmoplakin deficiency in a teenager with skin blistering, woolly hair and mild palmoplantar keratoderma. No variant in the genes causing EBS was identified. An arrhythmogenic right ventricular cardiomyopathy is usually
associated with bi-allelic desmoplakin mutations. Cardiac evaluation is recommended even in asymptomatic patients to detect a cardiomyopathy.

This case highlights the importance of genetic testing in patients with PPK.
Abstract N°: 5016

Transcutaneous Electrical Nerve Stimulation (TENS) for Managing Pain in Hereditary Palmoplantar Keratoderma (PPK) – A Retrospective Case Series of 11 Patients

Alia Galadari*, Emmanuelle Bourrat1, 2, Geoffrey Hickman1, 2, Jean David Bouaziz3, Anne Blazy3


Introduction & Objectives:
Nonsyndromic hereditary palmoplantar keratodermas (nhPPK) is a collective term for a heterogeneous group of keratinizing disorders characterized by persistent epidermal thickening of the palmoplantar skin. No curative therapy exists, however, Acitretin can sometimes improve pain & thickness of PPK. Therefore, treatment aims at alleviating pain and improving functioning, thus improving quality of life. Due to localized painful attacks and the lack of efficacy of analgesics and topical treatments, we have proposed transcutaneous electrical nerve stimulation (TENS) utilization as an effective non-pharmacological pain reduction modality. Therefore, we present a retrospective case series of 11 nhPPK patients to assess the use of TENS in managing their pain.

Materials & Methods:
A descriptive retrospective case series was carried out at our reference center for genodermatoses of adult nhPPK (clinical and/or molecular diagnosis) treated with TENS between 03/2020 and 04/2023. We opted to use TENS to alleviate our patients’ neuropathic pain after treatment failure of appropriate conventional analgesics. The best analgesic result was obtained with the ‘gate control’ program (80 Hz–150 s or 100 Hz–200 s) and the TENS Eco2 device. Data collected included patients’ demographics, genotype, phenotype, co-morbidities, other medications consumed, as well as numeric pain scores (NPRS – Numeric Pain Rating Scale, DN4 – Douleur Neuropathique 4 Questionnaire, & NPSI – Neuropathic Pain Symptom Inventory) before and after TENS.

Results:
11 nhPPK patients have been treated (5 males and 6 females, with an overall mean age of 47 years). Common complaints reported by our patients in order of frequency include superficial burning sensation, deep compressive pain, paroxysmal stabbing pain, allodynia/hyperalgesia/somatization phenomenon due to rubbing or exertion of pressure, and paraesthesia (tingling) or dysesthesias. Furthermore, pre-treatment pain was also assessed: NPRS: varying between 6 and 8 out of 10, and DN4 with an average of > 5/10.

Of the 11 patients treated, 10 confirmed TENS effectiveness during the initial test. One month after TENS, three patients opted out, of whom two found it non-practical (i.e. choice of clothes) while the third found it difficult to wear. The seven remaining patients continue to use the TENS device (with a maximum duration of 24 months and a minimum duration of 3 months). The percentage of overall improvement reported was > 65% with NPRS. The pain improvement achieved by the device had a variable, lasting effect, allowing patients to become physically active for an average duration of two hours.

Conclusion:
This is an original abstract although TENS has already been used in the treatment of several itchy or painful dermatoses, there is no data in the literature to date linking TENS and nhPPK. Based on our case series, this non-invasive use of a TENS device suggests a non-negligible improvement and a decrease in NPRS. Despite no
reported adverse effects, the main limitation was the device’s size and cables, which can be inconvenient to wear for some individuals.

Nevertheless, more research is essential on a larger number of individuals in order to confirm the positive effect of TENS in reducing pain associated with PPK and gather more conclusive evidence. More research is also required to assess whether the use of TENS for several months or years would allow a long-term improvement in pain in this chronic genetic disease.
Multiple basal cell carcinomas and a novel CYLD gene mutation in a family with Brooke–Spiegler Syndrome

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Introduction & Objectives:
Brooke–Spiegler syndrome (BSS) is an autosomal dominant disorder caused by CYLD gene mutations and characterized by multiple adnexal cutaneous neoplasms. Malignant skin tumors arise in about 5-10% of cases, and basal cell carcinoma (BCC) is the most common one. Understanding of the pathogenesis of the skin tumor arising in BSS is limited.

Materials & Methods:
We studied four individuals from a two-generation family of Asian origin. In four family members, the diagnosis of Brooke-spiegler syndrome was made by clinical features along with genetic testing, and the skin tumors were diagnosed by histopathologic findings. Blood and tumor samples from affected individuals were collected after obtaining informed consent. Whole exome sequencing (WES) was undergone with blood samples of four different family members and two tissue samples of a single patient. Moreover, single-cell RNA sequencing (scRNA-seq) was employed to construct detailed cellular maps of the tumor tissue and compared with three normal hair follicle tissues and three typical BCC tumor samples.

Results:
WES sequencing of both the tumor and blood samples revealed a novel stop-gain mutation in exon 12, resulting in a large deletion of chr16:50815236-50816377. Through single-cell RNA sequencing (scRNA-seq), we identified that the CYLD-mutated tumor cell cluster overlapped with the hair bulge stem cell area as like typical BCCs, but with different pattern.

Conclusion:
We report multiple BCCs occurring in a two-generation family with BSS, and revealed a previously unidentified mutation in the CYLD gene. These multi-omics analyses allowed us to gain a more detailed understanding of the pathogenesis of the CYLD-mutated tumors.
Abstract N°: 5071

**Familial benign chronic pemphigus (Hailey-Hailey disease) with peculiar condylomata acuminata-like genital involvement**

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**Introduction & Objectives:**

Familial benign chronic pemphigus (FBCP), also known as Hailey-Hailey disease, is a rare genodermatosis with autosomal dominant inheritance and positive family history in 70% of the cases. The disease affects equally men and women and usually starts soon after puberty or in the third or fourth decade showing a chronic relapsing course. FBCP is caused by mutations in the ATP2C1 gene which encodes the human secretory pathway Calcium-ATPase (hSPCA1). This results in loss of keratinocyte adhesion and subsequent acantholysis. FBCP presents clinically with vesicles, crusted erosions, and rhagades in the flexural areas and rarely with genital verrucous papules that may be easily misdiagnosed as genital warts. We report FBCP with peculiar condylomata acuminata-like genital involvement.

**Materials & Methods:**

A 43-year-old woman complained from pruritic, erythematous papules, plaques and vesicles in the genital area of more than 10 years duration. She was ineffectively treated with antivirals, antimycotics and cryotherapy for a presumptive diagnosis of condylomata acuminata. In 2021, new multiple erythematous papules, plaques, and maceration zones appeared in the flexural areas on the neckline, axillae, groin and popliteal fossae. The patient’s brother and father suffered from similar skin lesions. The diagnostic workup included clinical recognition, histopathology of a skin lesion, direct immunofluorescence (DIF) microscopy and immunoserology for excluding pemphigus, as well as PCR for detecting human papillomavirus (HPV) DNA.

**Results:**

Routine laboratory tests were within the normal ranges. Histopathological examination revealed suprabasal clefting with acantholysis in the epidermis. DIF and immunoserological tests, including ELISAs for desmogleins 1 and 3 were negative. Moreover, HPV DNA testing was negative. Based on the clinical and laboratory findings, the patient was diagnosed with Hailey-Hailey disease. Treatment with systemic antibiotics, potent topical corticosteroids, and emollients resulted in a good therapeutic response.

**Conclusion:**

FBCP typically presents with vesicles, painful erosions, and rhagades in friction-prone skin folds. Annular, segmental, or generalized forms of the disease with lichenoid, psoriasiform or verrucous lesions have also been observed. Rare cases of isolated genital involvement are reported, mainly in women, where the wart-like appearance of the lesions may be clinically indistinguishable from condylomata acuminata as initially described in our patient. The theoretical possibility of FBCP coexisting with HPV infection, eczema herpeticum, or bullous pemphigoid requires histological verification and DIF to exclude other diseases and facilitate adequate treatment options.
High Intensity Focused Ultrasound (HIFU) treatment of Cutaneous Neurofibromas (cNF): Preliminary results from a prospective dual-center clinical investigation.

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Introduction & Objectives:

Neurofibromatosis Type I (NF1) is among the most common single-gene inherited conditions worldwide and predisposes to multiple forms of benign and malignant neoplasms. The most common tumor in NF1 patients is cutaneous neurofibroma (cNF). The benign cNF can appear in numbers up to several hundred on the skin of NF1 patients. cNF may cause pain, social and functional limitations. Treatment options include surgical removal or the use of various devices that cause tissue destruction showing limited efficacy and often leave cutaneous scarring. High intensity focused ultrasound (HIFU) is capable of controlled and targeted thermo-mechanical treatment to small intradermal volumes containing neoplastic cells, without inflicting damage to the surrounding tissue. The objectives of this study were to investigate safety, local tolerability, and efficacy of high intensity focused ultrasound (HIFU) for treatment of NF1 associated cNFs.

Materials & Methods:

Twenty adult patients having at least 8 eligible cNFs were recruited in two centers. Focused ultrasound treatment utilizing a 20 MHz HIFU-device with integrated dermoscopic guidance was performed using a handpiece with a focus depth of 2.3 mm below the skin surface. Single dose acoustic energy of 0.7 J/dose of pulse duration 250 ms/dose was manually positioned with distance of 1-2 mm between each applied dose, at repetition frequency of 1-2 seconds until the full cNF including a 1 mm perilesional margin was covered. No anesthetic was applied. Primary endpoint was evaluation of safety and tolerance of the HIFU-treatment. Post-treatment effects were assessed immediately after treatment and at follow-up visits including on-site clinical evaluation, patients' evaluation and clinical photography for 9 months. Further evaluation of the included cNFs was performed by ultrasound scanning (US) in one center and histopathology in the other center.

Results:

A total of 147 cNFs (mean 7.35/patient; diameter 2-9 mm) were treated. Mild wheal-and-flare reaction was observed immediately after treatment. Occasionally, erosions/crusts were observed and rarely dyspigmentation after 1 week and 3, 6 and 9 months post-treatment respectively. Regarding the primary endpoint, no serious adverse events occurred, and no significant scarring was observed. The median reduction in cNF thickness measured by ultrasound scanning was 0.53 mm with a range of -100% to +19%. Visual rating of treated cNFs by the clinical investigator at 9 months showed that 45 out of 92 cNFs (49%) had full or substantial reduction; biopsied lesions excluded. During treatment the patient-reported pain-score was median 3.5 (range 1-7) on a 0-10 point scale. No pain was reported post-treatment.

Conclusion:

HIFU treatment is a new non-invasive, rapid, and tolerable treatment modality. This study demonstrates the safety,
local tolerability, efficacy, and feasibility of HIFU for the treatment of cNFs. The variation in cNF reduction after HIFU-treatment and the occasional erosions and crusts in the treatment area indicate that dosing needs to be further adjusted. Follow-up clinical studies to optimize the dose response in adults with NF1 are underway with a goal of applying this therapy to both established and developing cNFs in the future.
Acrokeratoelastoidosis of Oswaldo Costa: a case report

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Introduction & Objectives:

Acrokeratoelastoidosis (AKE) of Oswaldo Costa is a rare autosomal-dominant genodermatosis with unknown cause first described in 1952 by Oswaldo Costa.

It’s a subtype of palmoplantar keratoderma which requires histopathology differentiation from other marginal and focal acral keratodermas and distinct disorders such as acrokeratosis verruciformis of Hopf. We present here a case report in which clinical and histopathological diagnosis can contribute to further medical education.

Materials & Methods:

A 34-year-old woman, presented with asymptomatic yellowish keratotic papules located symmetrically on the lateral areas of the palms, soles and dorsum of hands, since adolescence, with progressive worsening. Her daughter had similar lesions.

Our first hypothesis was of AKE and we have considered other marginal and focal acral keratodermas. A punch biopsy specimen was obtained from one of the papules on the palm.

Results:

Histopathological examination revealed orthokeratotic hyperkeratosis with epidermal acanthosis and hypergranulosis. In the dermis, there was discreet thickening of collagen fibers and elastic tissue stains demonstrated scant elastic fibers. These findings were consistent with acrokeratoelastoidosis.

Conclusion:

There are several entities that can develop palmoplantar keratoderma. Acrokeratoelastoidosis is a rare genodermatosis that is clinically characterized by asymptomatic multiple yellowish papules, sometimes glossy and keratotic or umbilicated, located symmetrically on the lateral areas of the palms, soles and dorsum of hands.

This disease typically begins during childhood and there is no racial or sex predilection. Both familiar and sporadic forms have been reported. Both autosomal dominant and recessive forms have been reported as well. Its cause is unknown, but it appears to have a relation to chromosome 2.

The clinical manifestations may result from an overproduction of filaggrin, which accumulates above the granular layer before being incorporated into the protein matrix of mature epidermal keratin.

Differential diagnoses include focal acral hyperkeratosis, degenerative collagenous plaques of the hands, keratoelastoidosis marginalis of the hands, acrokeratosis verruciformis of Hopf, and palmoplantar keratoderma of the punctate type.

The definitive diagnosis relies on histopathological examination which reveals orthokeratotic hyperkeratosis with epidermal acanthosis and hypergranulosis. Elastic tissue stains demonstrates a decreased number of elastic fibers which are fragmented (elastorrhexis).
The prognosis of AKE is good, apart from cosmetic concerns of some patients. Topical corticosteroids, salicylic acid, tretinoin, systemic prednisone or methotrexate, antibiotic therapy, and cryosurgery can be used with unsatisfactory results. However, patients must be informed about the nature of the condition and the limited treatment modalities.
Advances in treatment for Urbach-Wiethe disease: A systematic review

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Introduction & Objectives:

Urbach-Wiethe disease or lipoid proteinosis (LP) is a rare autosomal recessive genodermatosis caused by mutations in the ECM1 gene. This results in the deposition of hyaline-like material on the skin, mucosae, and internal organs. It is characterised by hoarseness and mucocutaneous lesions that develop in early childhood, such as acneiform scarring and verrucous hyperkeratosis.

We report a case of LP in a 48-year-old man with a good response to oral acitretin therapy.

Due to its rarity, there are no large clinical trials. Therefore, we have conducted a systematic review to summarize the available evidence on its therapy and help make better clinical decisions.

Materials & Methods:

We carried out a systematic review on PubMed, Web of Science, Cochrane, and Scopus databases using the PRISMA guidelines. The following search terms were used: ("lipoid proteinosis" OR Urbach-Wiethe) AND (treatment OR acitretin OR etretinate OR dimethylsulfoxide OR penicillamine).

Results:

Initially, 215 articles were found. After checking for duplicates and applying the inclusion/exclusion criteria, 26 studies were incorporated. Due to the lack of clinical trials, other designs of study, such as case reports, editorials, and case series, were included.

Oral retinoids: Acitretin administration showed variable clinical improvement. In our case, after six months of treatment, skin improvement was especially remarkable, with almost complete disappearance of verrucous plaques on the elbows and knuckles.

The literature included 24 patients treated with acitretin with a dose of 0.5 mg/kg for a median of 12 months. Of these, 16 (67\%) showed improvements in skin and 18 patients (75\%) in hoarseness. In one case, treatment was discontinued due to painful pyogenic granulomas.

Five patients were treated with etretinate 1 mg/kg/day for 2 months followed by 0.5 mg/kg/day for 4 months. Treatment was stopped in two cases due to gastric discomfort. Of the remaining 3 patients, 2 showed notable improvement, while one did not.

Dimethyl sulfoxide (DMSO): Four patients were treated with oral DMSO 60 mg/kg/day for 3 years. Only in one patient (25\%) was a minor overall improvement. Bad breath was observed in all patients.

Corticosteroids: They were used in one patient for 3 years with notable results. No side effects or analytical changes were observed.

D-penicillamine: One patient was treated with 600 mg/day for 2 years with modest improvement in skin texture.
and hoarseness. No side effects were observed.

Human placental extract: Two patients received intramuscular injections of human placental extract every two days. After two months, there was a significant improvement in skin and voice quality.

**Conclusion:**

Although further studies are necessary to provide more compelling evidence, we propose that low-dose acitretin may be an effective treatment for LP, showing fewer side effects than the other agents commonly reported in the literature.
Natural gene therapy by punch grafting of revertant skin in a recessive dystrophic epidermolysis bullosa patient with intractable ulcers.

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Introduction & Objectives:

Recessive dystrophic epidermolysis bullosa (RDEB) is a severe inherited blistering disorder caused by COL7A1 mutations, leading to lack of functional type VII collagen. People with RDEB suffer from chronic open wounds, significantly impairing their quality of life. Although numerous attempts have been made, the treatment for RDEB still primarily centers on wound care and managing symptoms. Revertant mosaicism (RM) is a phenomenon where cells carrying a germline mutation coexist with cells that have spontaneously corrected the mutation through a somatic reverse mutation. RM has been observed in various RDEB patients, and efforts have been made to transplant naturally corrected keratinocytes into unhealing wounds. Herein, we report the successful healing and sustenance of chronic open wounds by autologous punch grafting of revertant skin in a generalized severe RDEB patient.

Materials & Methods:

A 30-year-old female RDEB patient carrying compound heterozygous COL7A1 mutations (c.2922+2T>G, c.3139+12G>A) had a persistent 20 x 14 cm² ulcer on her upper back that remained unhealed for the past three years. We found a patch of revertant skin that did not exhibit blistering on the left forearm, which was confirmed by immunofluorescence and targeted deep sequencing. A total of eight sequential transplantations of revertant skin patches, obtained through 2 mm punch grafting, were carried out. For each session, 40 to 50 grafts were harvested, and the donor site healed within two weeks after each harvesting. The grafts were positioned in designated sections of the large chronic wound. The patient was hospitalized during transplantations and daily dressings were done. Afterwards, she received regular outpatient visits to a dermatologist with a one-week interval.

Results:

The transplanted punch biopsy specimens were successfully accepted in the grafted area without any major complications, and complete re-epithelialization of the lesion occurred within a period of two to six weeks. Epithelialization occurred not only in the grafted area but also in the surrounding region. The areas of re-epithelialization accounted for up to 360% of the grafted area. Immunofluorescence staining for collagen VII on sections from the donor and acceptor sites after 12 weeks demonstrated levels of collagen VII expression comparable to that of control skin. In contrast, the specimen from the mutant skin showed nearly no expression of collagen VII. During the 15-month course following the initial grafting, the grafted area remained intact, and her chronic ulcer progressively healed up. The patient experienced notable pain relief within the treated areas and reported an improvement in performing her daily activities.

Conclusion:

Our case clearly demonstrates that punch grafting of revertant mosaicism-occurring skin is an effective strategy for treating chronic RDEB wounds without the need for ex vivo genetic manipulation.
IgE levels in epidermolysis bullosa patients

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Introduction & Objectives: Pain and pruritus severely affect the quality of life in all dystrophic epidermolysis bullosa subtypes. Treatment of recessive dystrophic epidermolysis bullosa (RDEB) remains challenging, and new therapeutic targets are searched for in order to alleviate the pruritus and the chronic wounds. Elevated IgE levels have previously been reported in several RDEB patients and marked skewing of circulating Th2 helper cells can be linked to the increased itch (especially for DEB pruriginosa).

There are reports that suggest that anti-IgE therapy, and also therapy with monoclonal Ab that block the Th2 cytokines could help the inflammation associated with RDEB.

The objective of this study was to determine the proportion of subjects with increased serum levels of IgE in our EB cohort of patients.

Materials & Methods: a retrospective study was conducted and our cohort of 38 EB patients was reviewed regarding the type of EB, clinical presentation, diagnosis, immunohistopathological findings and biological characteristics (including the presence of elevated serum IgE).

Results: For the** 38 patients that were included in the study the average age was of 17.7 [range 1-67], with 25 children and 13 adults, 21 patients with RDEB, 16 patients with simplex EB and 1 patient with EB aquisita. Eight patients (21%) had increased serum levels of IgE (1 patient with Simplex EB, 7 patients with RDEB). One RDEB patient also had been diagnosed with atopic dermatitis and multiple allergies.

Conclusion: The subjects with elevated serum level of IgE had also higher clinical severity scores and accentuated pruritus compared to the patients with the EB subjects with normal IgE level.
Abstract N°: 5513

Identification of 15 Novel Mutations in the COL7A1 gene through Genetic Screening of 50 Epidermolysis Bullosa-Affected Indian Patients

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Introduction & Objectives: Epidermolysis bullosa (EB) is a rare and heterogeneous hereditary condition affecting the skin and mucous membranes. EB is characterized by skin fragility, leading to blistering and tearing with minimal friction. This study aimed to collect EB patients across India, perform targeted gene panel sequencing, and assess the correlation between genotypic and phenotypic expressions.

Materials & Methods: A single-centre, retrospective study in the Department of Dermatology at the Postgraduate Institute of Medical Education and Research (PGIMER) in Chandigarh was conducted. The whole study was conducted after obtaining ethical clearance from the Institutional Review Board and informed consent from the patients before initiation. A total of 50 patients with a clinical diagnosis of EB were seen between 2019 to 2022, from the Outpatient Department of Dermatology. Baseline demographic data, birth history, family history, skin manifestation at birth, past medical history, current cutaneous manifestations, and the evolution of the disease were assessed. Genomic DNA was screened for mutations using targeted gene panel sequencing of 23 genes related to EB, and genetic analysis was performed.

Results: In the current study, a total of 50 patients were subjected to targeted gene panel sequencing. Genetic analysis of 50 patients revealed 16 individuals with recessive form of DEB (32%), 12 individuals with junction epidermolysis bullosa (24%), and 10 individuals with epidermolysis bullosa simplex. Eight patients out of all sequenced patients were observed with the condition of dominant dystrophic epidermolysis bullosa (DDEB: 16%), while two were with Kindler EB (4%). The remaining two patients’ DNA samples failed to be sequenced. 7 new and 3 previously known mutations were observed in DDEB patients, while RDEB patients revealed 12 new and 4 previously known mutations. Out of 12 RDEB patients, 7 patients (58.33%) revealed compound heterozygous mutations, while 5 patients (41.66%) revealed homozygous alterations in the COL7A1 gene. The patients with JEB were observed with mutations in the LAMB3, LAMC2, and COL17A1 genes. EBS patients were observed with missense heterozygous mutations in the KRT5 gene. The patients with Kindler EB revealed heterozygous mutations (one is a splice-site mutation and the other is an insertion mutation) in the FERTM1 gene.

Conclusion: This study represents the largest investigation focusing on the clinical and molecular aspects of an epidermolysis bullosa (EB) cohort in India. Our observations indicate a relationship between genotype and phenotype, consistent with earlier studies, revealing the wide range of clinical manifestations and identifying new disease-causing genetic variations. Interestingly, our study yielded different results regarding genotype prevalence compared to existing literature. However, given the rarity of EB and our limited sample size, additional case collections are necessary to establish a robust genotype-phenotype association. In conclusion, our findings provide valuable insights for future clinical assessments and the potential implementation of stratified management approaches.
VDR polymorphism Cdx-2 and Fok-1 follow distinct inflammatory pathways in CI patients.

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VDR polymorphism Cdx-2 and Fok-1 follow distinct inflammatory pathways in CI patients.

Introduction & Objectives: Congenital ichthyosis (CI) is a group of monogenic disorders characterised by cornification due to mutations in genes involved in keratinocyte differentiation and epidermal barrier function. In last few years, studies have linked pathophysiology of these ichthyosis form disorders with Th1/17 inflammatory pathways. Besides, development of vitamin D deficiency and rickets in patients with congenital ichthyosis have recently been observed, yet exact cause of such association is not properly understood. Since in our previous studies, only Cdx-2 and fok-1 were found to be associated with CI, the objective of this study was to identify if Cdx-2 and fok-1 polymorphism in CI patients follow similar or distinct inflammatory pathways that might subsequently be associated with inflammation and rickets in these patients, respectively.

Materials & Methods: Congenital Ichthyosis patients (age and gender matched) were screened for four types of polymorphism commonly associated with Vitamin D Receptor (VDR) i.e. Bsm-1, Cdx-2, Fok-1 and Taq-1α (in 56 CI patients and 40 controls). The technique used was Restriction fragment length polymorphism (RFLP) where sequence of these polymorphisms was first amplified using PCR with gene specific primers, and this was followed by digestion of amplified products with specific restriction enzymes. The restricted fragments were then analysed for their molecular weight to identify the type of mutation (wild type, heterozygous type or homozygous type). Amongst these, only Cdx-2 and Fok-1 were found to be associated with CI. In another set of experiments, comparison between different cytokines of various inflammatory pathways (Th-17, Th1/2, etc) in Cdx-2 polymorphism (hetero type and wild type) and Fok-1 polymorphism (hetero type and wild type) CI patients were studied using RT-PCR.

Results: Results of RFLP and RT-PCR revealed that Cdx-2 and Fok-1 polymorphism patients had distinct inflammatory pathway cytokines involved. Cytokines associated with Th-17 pathway were found to be associated with Cdx-2 polymorphism, whereas, IL-4 and IL-6 were significantly associated with Fok1 polymorphism. On the other hand, no association between Bsm-1 and Taq-1α was observed.

Conclusion: Based on our results, following could be concluded:

- In CI patients, Th-1/Th-17 (cell mediated immunity) pathway was found to be associated with Cdx-2 polymorphism, whereas Th-2 (humoral mediated) with Fok1 polymorphism.
- Since immune modulation of ichthyosis is mainly IL-17 predominant, our results indicate that probably it is due to overlapping of Cdx-2 and Fok-1 polymorphisms in most of the CI patients.
- Few studies also show that IL-4, IL-6 interferes with bone mineralization and that Fok-1 polymorphism affects bone mineralization, hence Fok-1 polymorphism might be one of reasons why rickets is observed in few CI patients.
Abstract N°: 5648

Acrokeratoelastoidosis: about two exclusively plantar cases

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Introduction & Objectives:

Acrokeratoelastoidosis (AKE) is a rare and benign dermatitis described by the dermatologist Costa. It is an autosomal dominant genodermatosis, although it can occur sporadically. Characterized by papules or plaques on the lateral part of the hands and feet. We report 2 cases of exclusively plantar AKE.

Case reports:

Case 1

A 28-year-old female patient presented with painless and non pruritic plantar lesions that had been evolving for 2 years. The physical examination found three patches of different sizes, rough and translucent, the largest measuring 4 cm in length, located on the lateral and medial sides of the feet. The palmar examination did not find any lesion.

Biopsy was performed, showing hyperorthokeratosis, hypergranulosis and elastorrhexis in favor of AKE. Treatment was based on salicylic acid and tretinoin with medium improvement.

Case 2

Patient aged 20 years, who presented with skin lesions evolving for 1 month, located on the lateral and medial sides of the feet.

The dermatological examination revealed three well limited, translucent, round and oval plaques, centimetric in size, the largest one measured 2 cm, located on the lateral and medial sides of the feet.

Histological study of a plaque showed hyperkeratosis, hypergranulosis, acanthosis and fine and fragmented elastic fibers confirming the diagnosis of AKE. Our patient was treated with urea and tretinoin without any improvement.

Discussion:

AKE is a type of marginal keratoderma that primarily affects the lateral aspect of the palmoplantar regions. Because of the rarity of the disease, the exact incidence of the disease remains unknown. Although sporadic cases exist as in our two patients, AKE is an autosomal dominant genodermatosis.

Triggering factors have been described as repeated trauma, excessive sun exposure.

Clinically, it presents as multiple firm papules, small, round to oval, flesh-colored or yellowish with rough and keratotic surface located on the lateral and medial sides of the hands and feet. The lesions are usually bilaterally and symmetrically distributed, although unilateral involvement has been reported.

Histological findings are hyperkeratosis, hypergranulosis, mild acanthosis, homogenization of collagen, and alterations in the elastic fibers of the dermis, which are fewer, thin, and fragmented.

The different treatment modalities tried:
Topical by emollients and keratolytic agents including salicylic acid, urea, sulfur, tretinoin and dermocorticoids.

Oral by corticosteroids, antibiotics, dapsone, methotrexate, isotretinoin, acitretin and physical by cryotherapy, laser or surgery.

**Conclusion:**

AKE is a rare condition characterized by clustered, small, firm papules distributed on the margins of the hands and feet. The most common histopathologic findings of AKE are hyperkeratosis and degeneration of elastic fibers. Different treatments have been used to treat AKE without much success.
Abstract N°: 5698

Case report: rare type II segmental piloleiomyomas

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Introduction & Objectives: Leiomyoma was first described by Virchow in 1854 as a benign growth of smooth muscle tissue. Cutaneous leiomyomas are categorized based on 3 sites of origin: blood vessel walls (angioleiomyomas), muscle genitalia and erectile tissue of the nipple (genital/dartoic leiomyomas) and the arrector pili of the skin (piloleiomyomas/pilar leiomyomas).

The piloleiomyomas are the most common subtype. They can appear as solitary, multiple disseminated, segmental or zosteriform and blaschkoid patterns. Segmental or zosteriform leiomyoma can occur either alone (Type I), or with scattered non segmental lesions elsewhere (Type II); the latter subtype occurring rarely.

A loss of function mutation in the gene encoding fumarate hydratase on chromosome 1q has been found to predispose individuals to Type II segmental leiomyoma. Reed’s syndrome or MCUL (multiple cutaneous and uterine leiomyomas)/HLRCC (hereditary leiomyomatosis and renal cell carcinoma) has been found to be caused by germline mutations in fumarate hydratase (FH) in the majority of screened cases.

Materials & Methods: A young 32 years old man consults in our clinic for pinkish-red nodules on his back, very sensitive to cold water and pressure. The lesions appeared at the age of twenty, but their appearance and symptoms have worsened recently since starting a new sport activity.

He has no medical personal or family history to report.

The skin examination reveals unilateral, firm, skin coloured papulo-nodular lesions with a zosteriform distribution on the right scapular and thoracic area and two recent solitary nodules on the right shoulder with a positive pseudo-Darier sign.

Results: A punch biopsy was performed, revealing a normal epidermis, mesenchymal spindle-cell nodules located in the dermis, composed of elongated cells of eosinophilic cytoplasm and ill-defined boundaries, spindle-shaped nucleus and blunt edges, forming multiple cell bundles with well-defined boundaries, minimal lymphocytic infiltrate and one mitosis noted. The immunohistochemistry concludes diffuse staining of alpha-actin and desmin. The Ki67 is low.

Due to the rare zosteriform distribution and the appearance of new nodules, further investigations were performed to rule out a Reed Syndrome or other several associations described in the literature (dermatite herpetiforme, MEN type I, polyposis intestinale, leucemie lymphoide chronique, VIH).

The complete blood count, thyroid panel, HIV testing, urinalysis and renal ultrasound were completely normal. The genetic consultation concluded no familial leiomyomatosis and no need for a gene mutation testing for fumarate-dehydrogenase, but he was advised regular follow-up to detect any sign of renal cell carcinoma early.

Conclusion: The patient was counseled regarding the treatment options and he refused the oral treatments, accepting a topical anesthetic cream before sport activities. The cause of pain is unclear and it is thought to be a result of either smooth muscle contractions or dense nerve fibers bundled within the tumor. Genetic and environmental modifying factors play a role in predisposition to renal cancer in MCUL, therefore a genetic
counseling and a regular follow-up is mandatory for this type of condition.
Abstract N°: 5715

Multiple familial trichoepithelioma - a case report

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Introduction:

Multiple familial trichoepithelioma is a rare autosomal dominant inherited disease characterized by the presence of multiple cutaneous neoplasms of follicular origin known as trichoepitheliomas, commonly found on the face, cervical region, and scalp. This disease is caused by mutations in the CYLD gene, which is responsible for regulating cell growth and division.

Case report:

We describe the case of a 39-year-old woman with no significant medical history, referred to our dermatology department for cutaneous lesions on her face that had been present for 10 years, progressively increasing in number and occasionally pruritic. She reported a family history of similar lesions in her mother, as well as in one brother and one sister.

On physical examination, numerous yellowish-white, round papules with smooth surface and well-defined borders were evident, measuring approximately 3-4 mm in diameter, located around the nose and on the upper lip. A skin biopsy was performed on one of the lesions, and the histopathological result revealed characteristics consistent with a trichoepithelioma. Given the clinical suspicion of a genodermatosis, a genetic study targeting the CYLD gene was requested, which revealed a frameshift mutation (p.Ser366fs) in heterozygosity, classified as probably pathogenic and not previously described in the literature. Thus, the diagnosis of familial multiple trichoepithelioma was established.

Destructive treatment of the lesions using electrosurgery was proposed to the patient and periodic sessions have been maintained since then.

Discussion:

This case illustrates a diagnosis to consider in the presence of multiple cutaneous lesions, particularly on the face, especially in patients with a positive family history. The diagnosis of this disease is based on clinical presentation, family history and complementary diagnostic examination, such as genetic testing, in which we found a new mutation, and histopathological analysis of the cutaneous lesions. Treatment is symptomatic and primarily surgical. The occurrence of malignant lesions is rare. However, given the possibility of malignancy, as well as the continuous growth of multiple lesions in cosmetically sensitive areas, regular follow-up of these patients is advised.
Encephalocraniocutaneous lipomatosis - case report of a rare congenital condition

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Introduction & Objectives:

Encephalocraniocutaneous lipomatosis (ECCL), also known as Fishman syndrome, is a rare congenital neurocutaneous disorder characterized by intracranial, facial, and/or cervical lipomas, ocular lesions, and brain abnormalities. We report a case of this condition.

Materials & Methods:

Retrospective review of medical records from a newborn diagnosed with ECCL.

Results:

We describe the case of a full-term male newborn with no history of complications during the mother’s pregnancy. The baby was delivered by cesarean section and referred to our service due to congenital scalp lesions.

On the initial physical examination, five days after the delivery, pseudo-vesicles were observed bilaterally in the parietal region, measuring between 2 and 5 mm, with a yellow-orange color. During follow-up, these pseudo-vesicles evolved into hairless, erythematous and oval-shaped areas of variable sizes, some of which were covered with a pseudomembrane in the temporo-parietal regions. Ocular examination revealed bilateral perilimbal and temporal conjunctival light-red lesions suggestive of conjunctival choristoma, as well as an indentation of the right upper eyelid. Fundoscopy demonstrated bilateral, irregular, hypopigmented, creamy-white peripapillary and peripheral chorioretinal lesions.

A skin biopsy was performed on one of the hairless areas, which revealed findings consistent with psiloliparus nevus. A neuro-axis magnetic resonance imaging (MRI) was also requested, showing lipomas adjacent to the right trigeminal nerve and left cortico-subcortical temporal region, as well as leptomeningeal enhancement in some areas and enlargement of the extra-axial space in the fronto-temporo-parietal region. The definite diagnosis of ECCL was established based on the clinical and imaging findings, which met the diagnostic criteria established in literature.

The patient is currently under clinical surveillance, and thus far, his development is considered within the normal range.

Conclusion:

Our case is illustrative of ECCL. Patients with this syndrome, which occurs due to sporadic mutations in the FGFR1 gene, typically exhibit marked developmental delay, along with epilepsy, limb spasticity, and characteristic cutaneous and ocular changes. Diagnosis is predominantly clinical, supported by imaging and histopathological examinations. Treatment is primarily conservative, as there is no established cure. Early clinical suspicion and a multidisciplinary approach are needed for accurate diagnosis, management, and follow-up.
Abstract N°: 5768

Epidemiological and clinical features of Bloom’s syndrome in 9 Tunisian cases

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Epidemiological and clinical features of Bloom’s syndrome in 9 Tunisian cases

Introduction:

Bloom’s syndrome (BS) is a rare autosomal recessive genodermatosis caused by germline mutation of the BLM gene. BS is characterized by short stature, sun-sensitive, red rash, mild immune deficiency with increased susceptibility to infections and, most importantly, to many types of cancer.

Materials & Methods:

We conducted a retrospective cohort study from 1990 to 2021, in which we collected nine BS at the department of dermatology of the university hospital of Sfax (TUNISIA). The diagnosis was confirmed by genetic tests in all cases.

Results:

We collected 9 patients with a mean age of 19 years (6-41 years). The sex ratio F/M was 1.25. For all patients, the parents were consanguineous. The telangiectatic erythema was developed in all the patients between 6 months and 2 years old on the cheeks, on the nose, on the lips and the lower eyebrows. The photosensitivity was constant and was complicated by vesiculas and bullae for 5 patients who had extensive lesions. The growth deficiency observed for all patients. It was marked, between −2 and −4 DS (standard deviation). The number of sister chromatid exchange was increased to twelve-fold comparatively to normal subjects. Two patients developed a breast cancer; the evolution was fatal in one. One patient developed a leukaemia, the evolution was also fatal. And another patient developed a colon cancer.

Discussion:

The main clinical features of the BS are prenatal onset proportionate dwarfism, telangiectatic erythema and photosensitivity. All these cardinal clinical aspects were found in our patients.

Neurological disorders are frequent, mainly major microcephaly described in most of the reported cases. In our series, two patients suffered from a mild mental retardation. Duplication of ureter and renal ectopy were also reported.

The risk of occurrence of neoplasia is a major concern for BS patients (44% of our patients). Solid tumors are the most common cancers involving the breast, uterus, larynx, colon, followed by leukemia.

Conclusion:

BS is an inherited disorder that can be fatal. The high rate of consanguineous marriages in our country would favor the occurrence of the disease.
Abstract N°: 5828

**Bushy Baby- A rare case of Cornelia De Lange Syndrome**

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**Introduction**

Cornelia de Lange syndrome (CDLS) is a rare genetic condition with developmental disorder and malformation affecting multiple systems. The incidence varies from 1:10,000 to 1:50,000 live births with no racial predilection. It is associated with congenital anomalies, growth retardation, neurodevelopmental delay, dysmorphic facial appearance, hypertrichosis, and skeletal anomalies. Most of the cases are sporadic while few of them have autosomal dominant inheritance (26-56%) involving NIBPL gene (chromosome 5) and SMC1A gene (X chromosome). There is no definitive biochemical or chromosomal marker for the prenatal diagnosis. The disorder is present from birth, but it is not always diagnosed at birth. The diagnosis is made clinically through signs and symptoms observed by the clinician with detailed history, physical examination, and laboratory tests.

**Case Report**

A 7-year-old girl, term, non-consanguineous parents, was referred from pediatric OPD for excessive hair growth over her body since birth. The child demonstrated low anterior and posterior hair line, hypertrichosis over face, back & extremities. On further examination, facial features revealed bushy eyebrow, synophrys, long curled eyelashes, depressed nasal bridge, long philtrum, thin upper lip, micrognathia along with clinodactyly of fifth finger. Anthropometry showed stunting (-2 SD), microcephaly (-2 SD) and low weight (-1 SD). History revealed low birth weight, delayed milestones, autistic behavior, decreased response along with history of recurrent generalized tonic clonic seizure for last 4 months. The child underwent further investigation guided by the complaints. Baseline investigation were within normal limit while EEG demonstrated abnormal pattern. MRI (brain) showed ischemic insult in bilateral periventricular white matter. Otoacoustic Emission demonstrated loss of outer hair cell function suggestive of cochlear deafness. X ray (Hand & wrist) showed short left 5th metacarpal and phalynx and non-visualization of distal epiphysis of both Ulna whereas Orthopantomogram revealed oligodontia. The diagnosis of Cornelia de Lange Syndrome was made based on clinical diagnostic criteria formulated by CDLS Foundation.

**Discussion:**

CDLS is a rare syndrome but have well defined clinical features. The diagnosis is primarily clinical based on signs & symptoms including growth retardation, facial dysmorphism, short stature, hypertrichosis, phalangeal abnormalities, and psychomotor delay. Life expectancy is normal if no major systemic malformation occurs. A multidisciplinary team is required to diagnose & treat CDLS patients to improve the prognosis and quality of life. This case highlights the importance of thorough clinical examination in cases with any altered dermatological finding associated with systemic complaint.
Abstract N°: 5841

Corpus Callosum Abnormalities in Incontinentia Pigmenti - the Impact of the IKBKG Gene

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Introduction & Objectives: Incontinentia pigmenti (IP) is a rare X-linked genodermatosis with an estimated prevalence of 1.2/100,000. Primarily it affects females and is usually lethal in males. Mutation of the IKBKG gene localized on the X chromosome causes IP.

Materials & Methods: The most prominent clinical manifestations of IP are skin changes, representing major IP diagnostic criteria. Dental, ocular, and central nervous system (CNS) anomalies are considered minor criteria. CNS anomalies usually occur from the neonatal period and represent the most crucial threat to the everyday life of patients with IP. One of IP’s most frequent CNS abnormalities was corpus callosum (CC).

Results: Knowing the frequency of CC anomalies in IP and that the most frequent causes of ACC are gene mutations, the connection between their occurrence and gene mutations in IP patients should be investigated. This study aimed to determine the presence of CNS abnormalities, especially CC anomalies in IP patients, and their relationship with the IKBKG gene mutations, the possible presence of other gene mutations, and the X-chromosome inactivation pattern. For this purpose, genetic analyses of the IKBKG gene and the X-chromosome inactivation, as well as Magnetic Resonance Imaging (MRI), Next Genome Sequencing (NGS), and Whole Exome Sequencing (WES) analyses were performed on a group of seven patients with a clinically confirmed diagnosis of IP, according to the updated IP diagnostic criteria.

Conclusion: The simultaneous presence of IKBKG mutation and CC abnormalities and the absence of other mutations indicates that IKBKG may cause CC abnormalities and should be included in the list of genes responsible for CC abnormalities.
Abstract N°: 5854

Late-onset Papillon-Lefèvre syndrome

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Introduction & Objectives: Early** childhood is when Papillon-Lefèvre Syndrome (PLS) first appears, and it progresses to palmoplantar hyperkeratosis, an aggressive periodontal disease that affects both primary and permanent teeth. The initial clinical signs are periodontitis and primary tooth loss between the ages of 2 and 4, which are subsequently followed by palmoplantar hyperkeratosis and the loss of permanent teeth during adolescence. The CTSC gene, which produces the lysosomal protease cathepsin C, has been shown to have loss-of-function mutations in PLS. In this case, clinical PLS symptoms appeared at age 20, and we identified a heterozygous mutation in the CTSC gene. Despite the heterozygous mutation, this case was considered unusual because it had a late start and clinical symptoms. Here, we present an unusual case of late-onset PLS associated with a heterozygous mutation of codon 1047delA in the CTSC gene.

CASE: A 31-year-old female patient born to distant relative parents was admitted to the dermatology outpatient clinic with calluses on the soles of her feet and ankles but no known systemic illnesses. Dermatologic examination revealed yellow-hyperpigmented and erythematous hyperkeratotic plaques on the patient’s knees, elbows, feet, and ankles. There was zirconium coating where the upper incisors and upper canines were gone, along with erythematous and edematous gums. According to the patient’s anamnesis, a punch biopsy was done a year before, showing a layer of lamellar orthokeratosis, basal pigmentation, minor perivascular inflammation, psoriasiform hyperplasia in the epidermis, and a thin granular layer. She has been experiencing gum problems since she was 20 years old. There was no history of early primary tooth loss or periodontal disease in the patient. The clinical symptoms of the patient suggested Papillon-Lefèvre syndrome. A heterozygous mutation of codon 1047delA in the CTSC gene was found following a thorough gene sequence analysis. Based on genetic and clinical information, the patient was diagnosed with late-onset Papillon-Lefèvre syndrome. There was no family member with a similar history. Since the disorder is frequently autosomal recessive and the c.1047delA heterozygous mutation in the CTSC gene was found, the patient should have been a carrier and not shown clinical signs, yet late-onset clinical symptoms were seen.

Conclusion: Late-onset PLS, a very rare manifestation, may be associated with heterozygous CTSC mutations. In order to prevent the loss of permanent teeth, it is critical to identify the disease’s clinical indicators and make an early diagnosis.
Abstract N°: 5866

Skin–Heart Connection

Mihoub Bourakba

Introduction & Objectives:

Cardiocutaneous genodermatosis associate Palmoplantar keratoderma, Woolly hair and Dilated cardiomyopathy especially on the left ventricle side, and early morbidity.

Materials & Methods:

We describe three cases with atypical skin presentation.

Neither parent nor any other family member had any skin or ectodermal abnormalities

Case 1: A 2-year-old girl present Prominent focal hyperkeratosis of the palms and soles. As neonate she also had perioral fissuring and cheilitis and sparse scalp hair

Cases 2-3: Two siblings present hyperkeratosis, woolly hair with ectodermal fragility. Clinical examination show transient pruritic blistering on trunk and extremities, multiples erosions, spotaneous bullae and bisters were present

Results:

Genetic study revealed different new autosomal recessive mutations of desmoplakin gene associated with intermediate filament binding site of cells

ECG and Echocardiography were without abnormalities

Naxos disease/ carvajal syndrome: is a Cardiocutaneous genodermatosis associate Palmoplantar keratoderma Woolly hair and Dilated cardiomyopathy especially on the left ventricle side,

Conclusion:

Clinicians should be aware, if any child present with keratoderma of palm and soles with woolly hair since birth should evaluate for cardiomyopathy

Molecular genetic studies will continue to be important in identifying the mechanism underlying the phenotypes in these conditions
Abstract N°: 5960

Multiple familial trichoepithelioma - case report of a newly discovered mutation

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Introduction & Objectives:

Multiple familial trichoepithelioma is a rare autosomal dominant inherited disease characterized by the presence of multiple cutaneous neoplasms of follicular origin known as trichoepitheliomas, commonly found on the face, cervical region, and scalp. This disease is caused by mutations in the CYLD gene, which is responsible for regulating cell growth and division. We report a case of a patient with this condition and the discovery of a new associated mutation.

Materials & Methods:

Retrospective review of medical records from a patient diagnosed with multiple familial trichoepithelioma.

Results:

We describe the case of a 39-year-old woman with no significant medical history, referred to our dermatology department for cutaneous lesions on her face that had been present for 10 years, progressively increasing in number and occasionally pruritic. She reported a family history of similar lesions in her mother, as well as in one brother and one sister.

On physical examination, numerous yellowish-white, round papules with smooth surface and well-defined borders were evident, measuring approximately 3-4 mm in diameter, located around the nose and on the upper lip. A skin biopsy was performed on one of the lesions, and the histopathological result revealed characteristics consistent with a trichoepithelioma. Given the clinical suspicion of a genodermatosis, a genetic study targeting the CYLD gene was requested, which revealed a frameshift mutation (p.Ser366fs) in heterozygosity, classified as probably pathogenic and not previously described in the literature. Thus, the diagnosis of familial multiple trichoepithelioma was established.

Destructive treatment of the lesions using electrosurgery was proposed to the patient and periodic sessions have been maintained since then.

Conclusion:

This case illustrates a diagnosis to consider in the presence of multiple cutaneous lesions, particularly on the face, especially in patients with a positive family history. The diagnosis of this disease is based on clinical presentation, family history and complementary diagnostic examination, such as genetic testing, in which we found a new mutation, and histopathological analysis of the cutaneous lesions. Treatment is symptomatic and primarily surgical. The occurrence of malignant lesions is rare. However, given the possibility of malignancy, as well as the continuous growth of multiple lesions in cosmetically sensitive areas, regular follow-up of these patients is advised.
Abstract N°: 5969

Microsatellite instability in unselected cutaneous sebaceous tumours from a single centre over a nine year period: An interim analysis.

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Introduction & Objectives:

Lynch syndrome (LS) is a hereditary condition that increases risk of a variety of cancer types, including colorectal, ovarian, and endometrial cancers, as well as benign sebaceous tumours and skin cancers. LS usually arises due to germline pathogenic variants in mismatch repair (MMR) genes MSH2, MHS6, MLH1 and PMS2. The presence of sebaceous skin tumours has been linked with LS (and labelled phenotypically as Muir-Torre syndrome), and sebaceous tumours have the strongest association of all LS linked tumours with an underlying genetic diagnosis of LS. LS linked sebaceous tumours demonstrate microsatellite instability (MSI-high), a genetic signature of MMR. A limitation of existing work is that some prior studies have been ascribed from cohorts that may be enriched for LS families or utilised screening techniques that relied on loss of immunohistochemical (IHC) expression of mismatch repair proteins, which has been shown to be less sensitive in sebaceous tumours compared to colorectal cancer.

Our objective was to investigate the utility of two next generation sequencing assays that target microsatellites to determine the MSI status of an unselected series of sebaceous skin tumours.

Materials & Methods:

We obtained 119 unselected serial retrospective archive cases of sebaceous tumours (99 benign, 20 malignant) over a nine-year period from 2012 to 2021 from our institute pathology archive under ethical approval. 110 tumour samples had accessible FFPE tissue specimens and were included in the study. The samples were collected from a total of 45 female and 65 male patients, with a median age of 77 years and an interquartile range of 66 to 83 years. To interrogate the MSI status of the samples, we employed a recently published, molecular inversion probe (MIP) and amplicon sequencing-based assay targeting 62 microsatellites. For low input DNA samples (<50ng) we used a related multiplex polymerase chain reaction (PCR) and amplicon sequencing-based assay targeting 14 microsatellites.

Results:

We present interim results from 49 samples. 12 samples were successfully analysed using the MIP based assay and 37 with low input DNA were studied using the PCR based assay. 37% (18/49) of these sebaceous tumour samples were MSI-high; 10/18 samples were obtained from male patients and the average age at time of tumour excision was 75.7 years.

Conclusion:

The frequency of MSI-high sebaceous tumours detected using amplicon sequencing technologies is in keeping with prior estimates in cutaneous sebaceous tumours. We aim to investigate our MSI-high cases using somatic sequencing of MMR genes, and to correlate this with IHC expression of MMR proteins. Taken together, our work will inform the utility of sensitive MSI screening assays for the detection of sebaceous skin tumours that are
associated with LS.
Familial Lichen Planus: A Report of three Cases and Review of the Literature

Kaoutar Elmachichi, Laila-Zineb Chbihi-Moukit, Maryem Aboudourib, Oufae Hocar, Said Amal

Chu Mohamed Vi Marrakesh , DERMATOLOGY, Chu Mohamed Vi Marrakesh

Abstract N°: 5986

Familial Lichen Planus: A Report of three Cases and Review of the Literature

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Chu Mohamed Vi Marrakesh , DERMATOLOGY, Chu Mohamed Vi Marrakesh

Introduction & Objectives:

Occurrence of familial lichen planus (FLP) is not common, characterized by an early onset, prolonged course, involvement of oral mucosa and atypical clinical forms. Different enviromental or genetic factors have been investigated in its pathogenesis.

Here we reported a case of three members of a family affected with different form of lichen planus, the father and 2 sons.

Materials & Methods:

Case 1: A 55-year-old man suffered from an intense pruritic eruption since over 10 years, consisting of multiple violaceous confluent papules, about 1cm, extending bilaterally and symmetrically in the pretibial region with an hypertrophic appearance. and the dermatoscopy evidenced fine scales on an erythematous background and Wickham’s striae.

The clinical diagnosis of hypertrophic Lichen Planus was confirmed by histology, which revealed hyper orthokeratosis, acanthosis and papillomatosis, irregular epidermal hyperplasia and a band-like lymphocytic infiltrate in the superficial dermis.

Case 2: The patient’s 13 years old son began to suffer from a similar pruritic eruption since the age of 6 in the pretibial region but less extensive and not hypertrophic. The dermoscopy and the pathological examination showed features typical lichen planus.

Case 3: The second 9 years old son was admitted with an intense pruritic eruption since the age of 7, consisting of polygonal, violaceous papules, atrophic in some area, initially appeared on the pretibial area, gradually spread to the trunk and upper limb. The diagnosis of lichen planus was confirmed by dermoscopy and pathological examination.

Results:

The incidence of LP in the general population is between 0.1 and 1.27 %. It typically affects middle-aged adults of both genders with no evident sexual predilection. However, it can be observed at any age and some reports indicate a slight predominance in women up to a ratio of 2 : 1.

LP is usually sporadic, Although, there is a familial form of LP, reported in 1 to 4.3% of childhood LP series and the existence of familial cases of LP may suggest a possible genetic predisposition.

A study reported cases of familial lichen planus (FLP), developed within a period of 3 years, in 2 sisters as well as in the son of one of the women. Furthermore, Nanda et al reported the case of one girl with classic LP whose father had also similar complaints.

Previous reports of FLP cases as well as the long interval between onset of the disease in the affected members of the family speak in favor of a genetic predisposition. HLA typing revealed HLA DR in all 3 patients. There was no
increased incidence of HLA B7, HLA A3 or HLA A28.

The diagnosis of LP is based on the clinical presentation and should be confirmed by biopsy, if suspected.

FLP differs from the classical form clinically, with earlier age at onset, more generalized involvement, and more common mucosal involvement. There is an increased tendency for erosive, ulcerative and linear forms, with prolonged course and frequent relapses.

Conclusion:

FLP is a rare entity that seems to be related to genetic prédisposition. The reported cases of patients with LP from the same family supports the genetic etiopathogenetic factor.

Therefore, the majority of previous studies could not effectively demonstrate the association of LP with genetics.

Genetic inheritance of LP is a matter that must be confirmed by further studies.
Treatment of Hailey-Hailey Disease (Benign Familial Pemphigus) in a female patient using once-daily roflumilast cream 0.3%

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Introduction & Objectives:

Hailey-Hailey disease (HHD), also known as Benign Familial Pemphigus, is a rare genodermatosis with autosomal dominant inheritance and no current approved treatments. HHD is caused by mutations within the ATP2C1 gene leading to defective keratinocyte activity and barrier defect. The ATP2C1 gene codes for hSPCA1 (human secretory-pathway Ca2+/Mn2+-ATPase isoform 1) and regulates intracellular Ca2+ and Mn2+ concentrations. HHD presents as eroded erythematous plaques with rhagades (fissures in the skin usually in flexural areas) that develop from the rupture of vesicles or bullae, causing chronic pain. Lesions tend to occur in intertriginous locations, such as the neck, axillae, inframammary area, and genitals. Roflumilast cream 0.3% is a potent topical phosphodiesterase 4 (PDE4) inhibitor approved in 2022 by the FDA for the treatment of psoriasis, including intertriginous disease. The structural and mechanistic underpinnings for roflumilast’s higher affinity binding to PDE4, relative to other approved PDE4 inhibitors, has been elucidated by applying structural and computational biology techniques. Here we report a case of HHD treated with roflumilast cream 0.3% once daily (QD) for 5 weeks.

Materials & Methods:

A 46-year-old female with biopsy proven disease with clinical presentation on approximately 10-15% of her body with erosions on the trunk, inframammary, lower back and arms. Disease was uncontrolled with exquisitely painful presentation and minimal disease response or improvement with decades of prior treatments. Chronic pain, weeping, and bleeding had a negative impact on QoL which escalated during menses. Past treatments included systemic and topical agents; antibiotics, corticosteroids, calcineurin inhibitors, antifungals, retinoids, and benzoyl peroxide. While completing workup and mandatory 30 day hold prior to starting oral isotretinoin, treatment with roflumilast cream 0.3% QD as monotherapy was started.

Results:

Following 5 weeks of treatment, areas of raw skin had resolved with no weeping erosive plaques, including inframammary erosions. The assessment of overall disease severity improved to 2/10 (mild), which the patient reported to occur after 1 week. Affected skin had re-epithelialized with some post-inflammatory hyperpigmentation. The patient reported improvement in pain associated with HHD symptoms within 1-2 weeks of application, achieving 0/10 (no pain) for the first time since diagnosis.

Conclusion:

We report the case of a 46-year-old patient with HHD successfully treated with roflumilast cream 0.3% QD monotherapy after prior treatment failure. Improvement in the symptoms of HHD were observed by the patient within 1 week and documented clinically after 5 weeks. This report suggests reduction of inflammation treatment with a potent topical PDE4 could offer a treatment option for patients with HHD.

1Wang J, Bunick CG. J Investig Dermatol. 2023.143;S194. #1130
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Abstract N°: 6116

Dermoscopy of muco-cutaneous signs of Fabry disease: 2 observations

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Introduction & Objectives:

Fabry disease is a lipid storage disorder caused by a deficient α-galactosidase A leading to systemic of non-metabolized substrates in multiple organs and tissues. Early symptoms are often non-specific including acroparaesthesia, hypohidrosis, and gastrointestinal disturbances. Although present in other metabolic and non-metabolic conditions, angiokeratomas are considered the cutaneous hallmark of Fabry disease.

Materials & Methods:

We describe herein the dermoscopic patterns of cutaneous lesions associated with Fabry disease in two brothers highlighting the specific aspects of acral angiokeratomas that help distinguish them from acral petechia.

Results:

Two brothers, aged 25 and 31 years, previously diagnosed with Fabry disease respectively at ages 12 and 18, were referred to our department for clinical evaluation as part of their multidisciplinary assessment. On physical examination, both patients presented with multiple angiokeratomas on the umbilicus and genitalia. They appeared as small, dark red to blue-black macules and papules ranging from 1-3 mm in diameter. They formed clusters on the surface of the scrotal skin and were rather scarce and slightly hyperkeratotic on the penis. On the rest of the body, the lesions were sparsely distributed, isolated, and relatively few in number. Numerous pinpoint, red-purple, non-blanching macules on the palms and soles were also observed. The inner surface of the lower lip showed small, shiny, red, and moderately elevated papules that were consistent with angiokeratomas of the oral mucosa. No other abnormalities of the tongue, the palate, or the gingiva were observed. Dermoscopic examination of the scrotum and penis revealed multiple well-defined red and purple lacunae, sometimes separated by white septae. On the lips, dermoscopy showed multiple well-defined red lacunae regularly distributed along the lower lip vermilion. These lacunae were connected to vascular dilation along the vermilion border that weren’t readily discernible to the naked eye. These lesions appeared to be connected to upper dermal vessel tortuosities located on the cutaneous side of the lower lip. No dilations were noted on the upper lip. Dermoscopy of the acral petechia-like macules showed well-demarcated red to pinkish ovoid lacunae, 1-2 mm in size causing an enlargement of dermatoglyphic ridges. The lacunae did not fade when pressure was applied pressure.

Conclusion:

Although the dermoscopic diagnosis of cutaneous angiokeratoma is well-documented and can aid in early intervention, the dermoscopic characteristics of acral angiokeratomas have not been previously reported.
Abstract N°: 6211

Genetic disorders of cholesterol biosynthesis: Porokeratosis and beyond.

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Introduction & Objectives:

Genetic disorders of cholesterol biosynthesis result in a wide range of cutaneous phenotypes and can present at any age. Disseminated superficial actinic porokeratosis (DSAP), a dominantly inherited genodermatosis associated with cosmetically disfiguring lesions and a possible increased risk of skin cancer, is a prototype of this group of disorders. The genetic basis and pathogenesis of this and related genodermatoses are reviewed, and recent studies supporting a role for therapies that target cholesterol biosynthesis are presented. The pharmacology of topical statins and the treatment pipeline are examined, with implications for the therapy of rarer genodermatoses including congenital hemidysplasia with ichthyosiform erythroderma and limb defects (CHILD) syndrome, X-linked ichthyosis and SC4MOL deficiency.

Materials & Methods:

An open label, split-body clinical trial was conducted comparing topical simvastatin-cholesterol with bland emollients for treatment of adults with DSAP when used twice daily for 6 weeks. Approval was obtained from the UnitingCare Health human research ethics committee.

Results:

Eight patients with thirteen limb pairs were recruited, with a median dermatology life quality index of five. Bayesian ordinal logistic regression revealed significant improvement in lesion number, erythema, scale, and patient-reported disease activity in treated limbs.

Conclusion:

Topical simvastatin-cholesterol appears to be a safe and effective treatment for DSAP. Further studies are required to determine the optimal choice of statin, concentration and vehicle as well as the required frequency and duration of therapy to maintain remission. Emerging evidence supports the use of topical statins for related genetic disorders of cholesterol biosynthesis.
Identification of novel variants among Indian patients with Xeroderma Pigmentosum using next generation sequencing.

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Introduction & Objectives: Xeroderma pigmentosum commonly known as XP, defined by excessive sunlight sensitivity that causes symptoms such as sunburn, irritability, dry skin, spots, hyperpigmentation/hypopigmentation and ocular symptoms like photo-sensitivity, blurred vision, cataract and photophobia. Some affected patients experience neurological disorders. This disorder has the potential to be more than 1000 times the risk of developing basal and squamous cell carcinoma and malignant melanoma skin cancer type in the sun-exposed region compared to the worldwide population. The study aimed to collect XP patients across India, perform targeted next generation sequencing and evaluate the genotype-phenotype correlation and mutational spectrum of XP in a north Indian population.

Materials & Methods: A retrospective investigation study was carried out in the Department of Dermatology, Venereology and Leprology at the Postgraduate Institute of Medical Education and Research (PGIMER) in Chandigarh. After receiving ethical approval from the Institutional Review Board and patients’ prior informed consent, the entire study was carried out. Between 2020 and 2022, the Outpatient Department of Dermatology, Venereology, and Leprology examined a total of 4 patients with a clinical diagnosis of XP. Initial demographic data, family and birth history, skin manifestation at birth, prior medical history, photosensitivity, skin malignancies (basal and squamous cell carcinoma), and disease evolution were all evaluated. Genomic DNA was screened for mutations using targeted next generation sequencing of four genes related to XP, followed by genetic analysis.

Results: In the current study, a total of 4 patients were subjected to targeted next generation sequencing. Genetic analysis of 4 patients revealed an individual with a nonsense homozygous mutation in exon 3 of the ERCC6 gene (c.526C>T) in a patient with Cockayne syndrome type B (CSB), and one individual with Xeroderma pigmentosum group C (XPC) has a new frameshift homozygous mutation (c.1292_1293dupAA) in exon 9 of the XPC gene. Another individual with a novel splice region mutation (c.555+8A>G) on intron 4 of the XPA gene has been discovered in a patient with Xeroderma pigmentosum group A (XPA). One individual with a double heterozygous mutation was identified in a patient’s genome: a splice acceptor mutation in one allele of the ERCC6 gene, intron 20 (c.4063-1G>C), which causes Cockayne syndrome type B (CSB), and a missense mutation in the other allele of the ERCC2 gene, exon 19 (c.1774C>T), which causes Xeroderma pigmentosum, group D (XPD).

Conclusion: This research focuses on the clinical and molecular characteristics of a Xeroderma pigmentosum (XP) cohort in India. Our observations are consistent with earlier studies, revealing the wide range of clinical manifestations and identifying new diseases causing genetic variations. Interestingly, our study yielded different results regarding genotype prevalence compared to the existing literature. Double heterozygosity in Xeroderma pigmentosum has not been reported in the literature. Nevertheless, extensive case collections are required in order to demonstrate an adequate genotype-phenotype relationship, considering the rarity of XP and our small sample size. In conclusion, our findings offer valuable data for further clinical evaluations and the potential application of stratified approaches to management.
Introduction & Objectives:

Peutz-Jeghers syndrome (PJS) is an autosomal dominant disorder characterised by polyposis of the gastrointestinal tract, pigmentation of the skin and mucous membranes and a predisposition to oncological diseases. The association with epidermodysplasia verruciformis (EV) has not been reported in the literature. Generally, EV is an autosomal recessive genodermatosis characterised by the persistent presence of beta group papillomavirus (HPV) in the skin. Recently a new classification of EV has been proposed to distinguish a classical genetic form, a non-classical genetic form and an acquired form. The association between these two diseases has not been reported in the literature.

We report the first description of epidermodysplasia verruciformis associated with Peutz Jeghers syndrome in 2 siblings.

Materials & Methods:

This is a clinical case of two siblings with confirmed Peutz-Jeghers syndrome (PJS) whose diagnosis was based on clinical examination and histological confirmation.

Results:

A 16-year-old patient, without any notion of consanguinity, followed in pediatrics with his sister for Peutz Jeghers syndrome with digestive polyposis, admitted to our training for dyschromic lesions on the face, neck, trunk and upper limbs present since the age of 10 years and whose evolution was marked by the appearance of other asymptomatic lesions on the back of the hands and perioral for which he was referred. The clinical examination revealed multiple lentigines on the back of the nose, the lips, and on the palms, hyperpigmented macules on the lips and face, and millimetre-sized papules with keratotic surfaces on the back of the hands associated with a poorly defined pityriasis versicolor-like patch on the back, which was negative on Wood’s light. We thought of the cutaneous manifestations of his pathology or epidermodysplasia verruciformis given the dyschromic patch on the back. A skin biopsy was performed on the dorsal aspect of the hand and confirmed the diagnosis of epidermodysplasia verruciformis. Examination of his sister revealed the same clinical finding. Unfortunately, no genetic studies were performed in our patients.

Conclusion:

This case is also interesting because of the association between two rare entities as well as the interest of skin biopsy in confirming epidermodysplasia verruciformis in front of the appearance of pityriasis versicolor-like and keratotic papules in a patient with Peutz Jeghers lentigines.
Abstract N°: 6334

**Ungual porokeratosis: a case series of four patients**

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**Introduction & Objectives:**

Porokeratosis is a specific keratinization disorder that manifests clinically as well-demarcated annular or linear keratotic plaques of various sizes and forms and with distinguished histology showing cornoid lamella, which is a column of closely packed parakeratotic cells extending through the stratum corneum. Nail changes secondary to porokeratotic lesions involving digits are quite uncommon and rarely reported. The aim of this study was to describe and characterize clinical and dermoscopic features in ungual PK.

**Materials & Methods:**

We performed a descriptive prospective observational study that included all patients diagnosed with PK who besides their cutaneous lesions also presented PK affecting the nail unit, at our dermatology department over one year from 2020 to 2021. In all patients histopathological confirmation was obtained and dermoscopy of the nail fold images were provided using a digital microscopy system.

**Results:**

Four patients were included in this study. The mean age was 29 years, with a clear predominance of men 3 versus 1.

All patients had typical lesions of PK that were not limited to extremities, histopathological confirmation was obtained showing parakeratotic cornoid lamella.

Types of PK involved included: porokeratosis of Mibelli, linear porokeratosis and Porokeratosis plantaris, palmaris et disseminata (PPPD).

An exclusive acral presentation were founded in one patient.

Clinical nail compromise included increasing forms of increased severity of nail scarring and destruction: ridging, longitudinal splitting, pterygium, other finding included paronychia.

No patient presented with anonychia (complete loss of nail).

Dermoscopic features included: Ungual dystrophy, splinter hemorrhages, Irregular and erythematous lunula, pachyonychia.

**Conclusion:**

Porokeratotic nail compromise is very rare, progressively destructive and tends to cause irreversible nail changes that must be known and directly evaluated in patients with porokeratosis lesions involving digits. Our case series provide the first dermoscopical description of ungual PK, showing features that can help to detect nail changes so that early measures against PK can halt the disease process and any resulting permanent damage.
Clinician perspectives on genetic testing for familial melanoma

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Clare Primiero EADV 2023 Abstract

Introduction & Objectives: Genetic testing for hereditary melanoma is associated with improved sun-protective and screening behaviours with no evidence of test-related distress. Dermatologists and skin cancer clinicians are optimally placed to offer testing. We developed and evaluated a training program to upskill dermatologically-trained clinicians to offer hereditary melanoma testing. The objective was to capture clinician perceptions of the training program and the perceived utility and feasibility of integrating melanoma genetic testing into practice.

Materials & Methods: Clinicians were interviewed using a semi-structured guide, and transcripts were analysed thematically.

Results: Seven of the eight trained clinicians agreed to be interviewed. The training format was well received, and minimal feedback for improvements on content was suggested. Specifically, clinicians reported using newly acquired knowledge outside the clinical research study, secondary to greater confidence and comfort ordering and discussing genetic testing. The perceived benefits to their offering testing included positive impacts on patients’ melanoma risk awareness, and continuation of care. Clinicians expressed concern regarding potential for psychological distress or genetic discrimination and had practical concerns regarding their availability to offer testing in a busy clinic. Suggested solutions for integration into practice included video decision aids, involving nurses in consultations, and embedded genetic counsellors. There was a perceived need for clear guidelines outlining eligibility criteria, relevant costs, and Medicare rebates, and recommended follow up care for mutation carriers.

Conclusion: The training program was well received by clinicians who reported increased genomic confidence. Interventions which address clinicians’ limited availability in clinics are likely to accelerate wider implementation.
Abstract N°: 6400

Alopecia areata with renal dysgenesis

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Introduction:

Alopecia areata (AA) is a common cause of non-cicatricial alopecia characterized by focal areas of hair loss usually on the scalp, eyebrows, beard and moustache areas. In some, it can progress leading to complete loss of scalp hair. We are reporting one such case of alopecia areata with renal dysgenesis.

Case report:

A 15-year-old boy presented to the dermatology OPD with complaints of patchy loss of hair involving the entire scalp for the past 6 months. Except for antidiabetics for gestational diabetes, there was no history of any other drug intake in the antenatal period. Patient denied hair pulling. Dermoscopy of scalp showed black dots, yellow dots and broken hairs. Diagnosis of multifocal alopecia areata was considered. Patient was treated with multiple intralesional corticosteroid injections, minoxidil and short contact dithranol with no improvement. Hence, oral cyclosporin was considered and further investigations were done. Complete blood count was normal. Urine routine examination showed 30-40 /hpf of RBCs, 5-10/hpf of pus cells, few granular casts and amorphous urate crystals with 2+ albuminuria. Wet mount preparation of urine showed 4-5 pus cells without any bacteria. Ultrasound abdomen showed left sided dysplastic kidney with bulky right kidney showing grade 2 renal parenchymal disease. He was referred to the nephrologist for further management. Oral mini pulse betamethasone therapy was commenced and was advised regular follow up.

Discussion:

Alopecia areata (AA) is a type of non-scarring alopecia involving the scalp and/or body. It is one of the most common forms of hair loss seen by dermatologists and accounts for 25% of all the alopecia cases.

AA frequently occurs in association with other autoimmune disorders such as vitiligo, lichen planus, morphea, lichen sclerosus, atopic dermatitis, Hashimoto’s thyroiditis, hypothyroidism etc. AA is an autoimmune disease with interplay of genetic and environmental factors in the development and progression of the disease.

The genetic role for AA is based on positive family history, twin concordance, HLA associations and studies on animal models. In a study of 513 patients with AA, family history was seen in 32.9 % of patients, majority being in first degree relatives. A 42% concordance rate of AA in monozygotic twins and 10% in dizygotic twins has been reported in a cohort study. Various studies have demonstrated susceptibility genes and HLA associations with conflicting and heterogenous results in AA. Reduced expression of KRT82 gene has been recently found in AA. This gene is specifically expressed in the hair follicle in the anagen phase and when defective leads to perifollicular CD8 cell infiltration. HLA alleles such as DR alleles and some DQ8 alleles have been implicated.

AA in females has been associated with Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome. This syndrome is characterized by Mullerian duct agenesis with congenital aplasia of the uterus and vagina. All four cases reported till date had AA with mullerian duct anomalies but only one case was reported with right renal agenesis as an associated finding of MRKH syndrome along with alopecia.

Renal dysgenesis is improper development of kidneys. The exact cause is unknown although genetic mutations
and drugs taken by the mother such as anticonvulsants and ACE inhibitors have been implicated.

In our case of AA, renal dysgenesis might have been a coincidental finding but further studies are needed to rule out a genetic basis.
A severe case of generalized RDEB caused by nonsense mutations in COL7A1 with favorable response to early topical gentamicin treatment

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Introduction & Objectives:

Recessive dystrophic epidermolysis bullosa (RDEB) is an incurable, inherited skin disease characterized by skin fragility, blisters, erosions and scarring. RDEB is caused by mutations in the COL7A1 gene encoding type VII collagen, the major component of anchoring fibrils which bind the epidermis to the dermis. More than 1000 distinct mutations have been identified in RDEB patients, of which 30% are nonsense mutations. Nonsense mutations result in premature termination codons (PTCs) that cause a truncated or unstable type VII collagen. Recent studies have shown that gentamicin can induce PTC read-through and result in the production of full-length type VII collagen in RDEB patients with nonsense mutations. It has been successfully used topically, intradermally and intravenously to treat patients with RDEB or junctional EB.

Materials & Methods:

Physical examination, skin biopsy for immunostaining and blood sampling for next generation sequencing analysis (NGS) were taken from the patient and/or her parents (NGS only).

Results:

We report a case of female newborn presenting with extensive skin blisters and erosions since birth. The blisters were widespread on the trunk and extremities, were of variable size, often hemorrhagic and associated with a large erosion of the inner aspect of her left leg. The oral mucosa was also affected. Her finger- and toe-nails were absent or dystrophic. Numerous milia were noted on post-erosive areas. There was no pseudosyndactyly. She was the first child born from healthy, non-related parents.

Skin biopsy with immunostaining from non-blistered area showed dermal-epidermal separation and complete absence of type VII collagen staining.

Next generation sequencing analysis of the patient revealed the presence of the c.4894C>T (p.Arg1632*) variant in exon 51 in COL7A1 inherited from the mother and the c.6994C>T (p.Arg2332*) variant in exon 90 in COL7A1 inherited from the father.

Both variants are reported in the HGMD pro database and are predicted to be damaging because they lead to a premature stop codon. These results confirm the diagnosis of RDEB at the molecular level and predict a generalized and severe form of RDEB.
Topical treatment with gentamicin 0.1% ointment was started from the first month of life once a day to all open wounds until wound closure. Soft silicone dressings were also used. After several months of treatment, clinical improvement in wound closure was noticed in treated areas which were less prone to blister formation compared to non-treated areas.

Gentamicin treatment was continued for 16 months and had no effect on hearing or renal function. To improve healing of all skin lesions and mucous membranes, intravenous gentamicin treatment at 7.5mg/kg for 14 days was recently started in hospital. The efficacy and tolerance of this treatment will be evaluated and presented in the future.

Conclusion: We present a case of severe generalized RDEB, caused by compound heterozygosity for two nonsense mutations in \textit{COL7A1}. Molecular diagnosis allowed to provide genetic counselling to the parents, informing them of a 25% risk of recurrence at each pregnancy and that early DNA-based prenatal diagnosis was possible.

This is the first time that topical gentamicin treatment is applied so early in a newborn with generalized RDEB. Our experience shows a favorable evolution of treated areas with no side effects. This encouraged us to evaluate intravenous gentamicin to treat multiple skin areas as well as mucous membranes.
Abstract N°: 6551

**Developing CRISP/Cas-treatment for keratoderma due to keratin 9 mutation**

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**Introduction & Objectives:**

*Keratin 9* mutations are known to cause debilitating palmoplantar hyperkeratosis, e.g. in patients with the dominant-negative *keratin 9* mutation p.N161S (c.482A>G). In contrast, we report a previously unrecognized mono-allelic mutation of *keratin 9* p.E283X (c.847G>T), generating a STOP codon without symptoms or with blisters only developing after physical stress. Therefore, monoallelic expression of wild type *keratin 9* should be a feasible gene-editing goal for the severe form.

**Materials & Methods:**

We therefore tested, whether a STOP codon can be introduced into p.N161S by using a ribonucleoprotein based double-nickase approach in patient-derived keratinocytes. After harvesting clones with an intact wild type allele and a frameshift-induced STOP codon on the mutated strand we demonstrate improved keratin 9 integrity comparable to p.E283X or wild type cells as assessed by immunofluorescence staining.

**Results:**

Upon heat stress 90% of p.N161S keratinocytes exhibited abnormal keratin aggregates, whereas in p.E283X keratinocytes and in gene edited p.N161S keratinocytes the frequency of keratin aggregates was low. To evaluate the risk of unintended small insertions/deletions, we employed comprehensive CAST-Seq and NGS analyses, which did not reveal any off-target translocations or mismatches.

**Conclusion:**

Our results obtained in primary patient-derived cells transfected by carrier-free electroporation of double-nickase allele-specific ribonucleoproteins demonstrate restoration of keratin 9 intermediate filament integrity with an excellent safety profile and major therapeutic potential.
Oleogel-S10 reduces dressing changes burden in patients with epidermolysis bullosa

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Introduction & Objectives:

Epidermolysis bullosa (EB) is a devastating genetic disease characterised by skin fragility, and blister formation in response to minimal trauma. Management is focused on demanding wound care with frequent and painful dressing changes commonly required. EASE (NCT03068780) was a randomised, double-blind, vehicle-controlled clinical trial of Oleogel-S10 (birch triterpenes, also known as birch bark extract) conducted globally in patients with EB, and was the first trial to demonstrate clinical benefit of any agent in the disease. The objective of this analysis was to determine if Oleogel-S10 had an impact on dressing change frequency as well as time spent on dressing changes in EASE for patients with the highest burden, i.e. those with daily dressing changes at baseline.

Materials & Methods:

EASE enrolled 223 patients with dystrophic EB or junctional EB and ≥1 partial-thickness wound 10–50cm2 present ≥21 days and <9 months. Patients were randomized to receive topical Oleogel-S10 (n=109) or control gel (n=114), both with standard-of-care wound dressings. Frequency of dressing changes over time was considered important and was captured in EASE. A post hoc analysis was conducted to determine the change from baseline in frequency of dressing changes for the subset of patients who had daily dressing changes at baseline. As the time needed for dressing changes was not captured in EASE, published evidence on the time required for whole body wound care (Bruckner AL, et al. Orphanet J Rare Dis 2020;15:1) was used to calculate the time saved for the subset of subjects with daily dressing changes at baseline. An additional 66.7% of time spent by caregivers (defined by Bruckner et al) was added to the patient time to provide overall time spent on daily dressing changes and time saved at Day 90.

Results:

Forty-seven patients receiving Oleogel-S10 and 53 patients receiving control gel were undergoing daily dressing changes at baseline. For this cohort, 35.6% of those treated with Oleogel-S10 had a reduced requirement for daily dressing changes by Day 90 of the EASE trial (versus 10.6% for control gel). There was a mean reduction of 1.36±0.24 weekly dressing changes undertaken for Oleogel-S10 versus 0.41±0.23 fewer for control gel (difference −0.95±0.33; p=0.005). This equates to almost three fewer dressing changes every two weeks for patients treated with Oleogel-S10, versus almost one change for control gel. Using the Bruckner data to determine appropriate ratios, the estimated time saved on dressing changes per week for patients receiving daily dressing changes at baseline was 10.9 h for Oleogel-S10 (6.6 h for each patient and 4.4h for their caregiver/assistant) versus 4.0h for control gel (2.4h for each patient and 1.6h for their caregiver/assistant) (Figure).
Conclusion:

Oleogel-S10 significantly reduced the frequency of daily dressing changes versus control gel in EB patients with the highest burden, and this translated into a relative reduction in the calculated time spent on this procedure. The time saved with Oleogel-S10 has the potential to considerably reduce the negative impact of laborious and painful dressing changes in patients with EB.

Figure. Change from baseline in time required for dressing changes in the subgroup of patients with daily dressing changes at baseline in the EASE trial