BIODERMA CONGRESS REPORTS

WORLD CONGRESS ON RARE SKIN DISEASES 2026

Reports written by Lisa Maudet, dermatology resident at Nancy University Hospital.

Double blind double dummy randomised control trial comparing rituximab versus cyclophosphamide in severe types of mucous membrane pemphigoid

Report written by Dr Lisa Maudet (dermatology, Nancy)

Speaker: Pascal Joly (France)

Background

Mucous membrane pemphigoid (MMP) is a rare autoimmune bullous disease of the dermo-epidermal junction, characterized by predominant or exclusive mucosal involvement. Its incidence has **more than doubled over the past decade in France**, with the highest incidence observed in patients aged **80–85 years**, at approximately **10 cases per million inhabitants per year**.

The disease carries substantial morbidity and mortality, and in the absence of treatment may progress to esophageal and laryngeal stenosis, strictures, and blindness.

Given the severity of potential complications, effective treatment is essential to delay or halt disease progression. However, because of its rarity, large randomized controlled trials in MMP are lacking, and the evidence supporting current therapeutic strategies remains limited. Cyclophosphamide had until now been considered the most effective immunosuppressant for severe MMP, prior to the introduction of rituximab, an anti-CD20 monoclonal antibody. Although prior literature suggested that rituximab might be more effective than cyclophosphamide, no controlled trial had directly compared the two agents. This study represents **the first prospective, multicenter, double-blind, double-dummy randomized controlled trial conducted in MMP**.

Methods:

Patients were centrally randomized in a **1:1 ratio**, stratified according to the presence of ocular involvement. In the cyclophosphamide arm, patients received oral cyclophosphamide (**1–2 mg/kg/day**) for 6 months, dose-adjusted for comorbidities, followed by 6 months of reduced-dose maintenance therapy (**0.75 mg/kg/day**), together with two placebo rituximab infusions administered on Days 1 and 15 at Months 0 and 6. In the rituximab arm, patients received rituximab infusions on Days 1 and 15 at Months 0 and 6, together with oral placebo tablets.

Eligible patients were aged **18 to 80 years**, with newly or previously diagnosed severe MMP, diagnosed according to the International MMP Consensus criteria.

The primary endpoint was the proportion of patients achieving complete or partial remission at 12 months.

Complete remission was defined as the absence of inflammatory lesions, blisters, or erosions, together with the absence of new fibrosing lesions and/or no worsening of established fibrosing lesions.

Partial remission was defined as the presence of transient new inflammatory lesions, blisters, or erosions that healed within one week without treatment, together with the absence of new fibrosing lesions and/or no worsening of established fibrosing lesions.

Results:

A total of **92 patients** were randomized, with **46 patients per arm**. In the rituximab arm, five patients discontinued treatment, including three consent withdrawal and two severe adverse effects. In the cyclophosphamide arm, eleven patients discontinued: one consent withdrawal, four investigator decisions, three for other reasons (COVID-19 pandemic), two for severe adverse effects and one death.

The primary analysis was conducted in the **intention-to-treat population**, comprising all 92 randomized patients, with missing data imputed using a modified maximum-bias approach in which patients who discontinued or withdrew were classified as treatment failures.

In this intention-to-treat analysis, complete or partial remission at 12 months was achieved in **33% of patients** (n=15) in the rituximab arm compared with **13%** (n=6) in the cyclophosphamide arm (**p=0.0254**). Complete remission was observed in **24%** (n=11) of rituximab-treated patients versus **13%** (n=6) of cyclophosphamide-treated patients.

A per-protocol analysis, restricted to patients who completed the assigned treatment without major deviation through 12 months, showed complete or partial remission in **55%** (n=18/33) of patients in the rituximab arm versus **26%** (n=6/23) in the cyclophosphamide arm (**p=0.0342**).

Among patients with ocular involvement at baseline (64 of 92 patients, with outcome data available for 54, and balanced between arms owing to stratification), complete or partial remission at 12 months was achieved in **46%** (n=13) of the rituximab group versus **27%** (n=7) of the cyclophosphamide group.

With regard to tolerance, at least one adverse effect occurred in **74%** (n=34) of patients treated with cyclophosphamide compared with **50%** (n=23) of patients treated with rituximab (**p=0.0182**). Severe adverse effects occurred in **30%** (14%) of the cyclophosphamide arm and **32%** (n=15) of the rituximab arm (**p=0.822**), indicating no significant difference in severe adverse event rates between groups. Quality of life improved moderately from baseline to Month 12 in both arms (**p=0.0111**), with no significant difference observed between treatment groups.

Conclusion:

Rituximab was superior to cyclophosphamide for the treatment of severe MMP, with a higher rate of complete or partial remission at 12 months and a more favorable overall tolerance profile.

These results represent the first analysis of this trial; several secondary endpoints remain to be reported, including time to complete or partial remission, cumulative duration of remission periods, number of disease flares or relapses, time to flare or relapse, and the mean evolution of the Disease Activity Score from Week 0 to Week 104.

Critical analysis of this presentation:

Strenghts: The use of an **intention-to-treat analysis with a conservative imputation rule** (discontinuations classified as treatment failures) protects against attrition bias and avoids overestimating efficacy.

The consistency of effect size and direction across the **ITT, per-protocol, and ocular-involvement subgroup analyses** strengthens confidence that the observed benefit of rituximab.

Limitations:

Patients **older than 80 years were excluded**, despite this age group corresponding to the population with the **highest disease incidence** (mean age at onset 80–85 years). While the ethical rationale for this exclusion is understandable given the toxicity of cyclophosphamide in frail elderly patients, it substantially limits the **external validity** of the findings for the patients most commonly affected by MMP in real-world practice.

Epidermolysis Bullosa: To biopsy or not to biopsy?

Report written by Dr Lisa Maudet (dermatology, Nancy)

Speakers: Reuven Bergman (Israel) advocating for systematic biopsy and Martin Laimer (Austria) advocating against systematic biopsy

The case for biopsy as a first step to diagnose EB

According to current guidelines, the diagnosis of epidermolysis bullosa (EB) and its differential diagnosis rely, as a **first step, on routine skin biopsy**, which subsequently guides definitive diagnosis.

The speaker presented **four illustrative case studies** in which skin biopsy was a necessary step, not only to reach a diagnosis but also to **exclude relevant differential diagnoses**.

CASE 1: A 14-day-old neonate was admitted to the neonatal intensive care unit with acute respiratory distress and failure to thrive. Family history revealed no consanguinity, and both parents were healthy. The neonate presented with edema and plaques in the epiglottis and upper airways, together with multiple esophageal erosions. Cutaneous blisters subsequently developed. Histology showed a neutrophilic and eosinophilic infiltrate, making a diagnosis of EB unlikely. Additional workup included collagen IV staining and direct immunofluorescence (DIF), leading to a diagnosis of neonatal autoimmune subepidermal IgG/IgA blistering disease, an important autoimmune mimicker of severe EB.

CASE 2: A young girl presented with vesicles distributed along **Blaschko's lines** were suggestive of **incontinentia pigmenti**, confirmed on biopsy showing intraepidermal vesicles containing numerous eosinophil. The diagnosis confirmed by **genetic sequencing of the target gene IKBKG/NEMO**.

CASE 3: A neonate presented with **blistering of the buttocks**. A diagnosis of **epidermolytic ichthyosis** was suspected on skin biopsy and subsequently confirmed by **genetic mutation analysis**. This case illustrated the value of histology in **guiding targeted gene sequencing**: **superficial epidermolytic ichthyosis** is associated with mutations in *KRT2*, whereas classic **epidermolytic ichthyosis** is associated with mutations in *KRT1* or *KRT10*.

CASE 4: A biopsy performed on an infant with acral blistering revealed a case of ectodermal dysplasia–skin fragility syndrome. Histopathology provided key diagnostic clues: acantholysis together with intracytoplasmic perinuclear eosinophilic condensations.

In conclusion: comprehensive transmission electron microscopy (TEM) analysis and a targeted next-generation sequencing (NGS) gene panel, along with the requisite expertise, are available only in a limited number of specialized centers worldwide. To simplify EB diagnosis, TEM can be replaced by routinely processed skin biopsy, which helps narrow the subsequent molecular genetic testing panel.

Accordingly, routine skin biopsy should be the first diagnostic step in a blistering infant (and at any age), as it often leads to an appropriate differential diagnosis of EB. Immunostaining on paraffin-embedded sections may help subclassify EB into its three major forms (EB simplex, junctional EB and dystrophic EB), serving as an alternative to TEM for this purpose while further narrowing the molecular genetic testing panel. In emergency settings, a limited panel of antibodies for immunomapping on frozen sections can enable rapid diagnosis.

The case against biopsy as a first step to diagnose EB

EB diagnosis requires accuracy, since subclassification informs early prognostication, clinical management, surveillance planning, trial eligibility, precision medicine, and genetic counselling.

Limitations of Biopsy-based techniques:

- They are *invasive and distressing* for patients, and a proportion of biopsies prove unsuccessful or non-contributory. For this reason, Speaker 2 argued that routine histology should be used to eliminate differential diagnoses rather than to establish a definitive diagnosis.
- The *specificity of biopsy-based techniques is insufficient*, and **sensitivity can be limited** in certain cases. **Electron microscopy**, while informative, is **expensive**, requires substantial **infrastructure and expertise**, is **operator-dependent**, and its **availability varies** considerably between centers.

Advantages of Genetic Testing:

- In contrast, *genetic testing is less invasive*, as it can be performed on a **blood sample, buccal swab, or saliva**. It offers **greater precision**, enabling diagnosis **at an early stage** with **unmatched resolution** and direct **proof of pathogenicity**. Genetic testing also allows for **genetic counseling**, including determination of the **inheritance pattern**, **risk calculation for future pregnancies**, and detection of **post-zygotic mosaicism** or **carrier status**.
- Methodological advancement has increased the feasibility of genetic testing, with reduced turnaround times (on the order of days to weeks) and falling costs within an increasingly dynamic genomic landscape, supported by broad commercial diagnostic capacity and improved funding, reinforcing its role as a reference standard. Genetic testing can further discriminate between dominant and recessive inheritance, identify mild phenotypes, and delineate specific disease subtypes.

In conclusion, genetic testing is increasingly regarded as a reference standard. Ongoing technical progress and declining costs continue to improve the availability, accessibility, and feasibility of genetic testing.

Nonetheless, important **limitations persist**:

- genetic testing provides no direct information at the protein level, and the functional consequences of splice-site mutations on the open reading frame remain unpredictable.
- Owing to variable genotype–phenotype correlation, genetic testing may at times fail to discriminate between disease subtypes.
- Diagnostic interpretation is also more challenging in underrepresented populations, as testing efficacy relies on the availability of regional genomic reference data.

The challenges of rare skin diseases with café au lait macules (CALM)

Report written by Dr Lisa Maudet (dermatology, Nancy)

Speaker: Elena Pope (Canada)

Approaching a child presenting CALM

Key questions to ask during the consultation: Does the child have any recognisable syndromic features? What other clinical or historical information is needed? Is additional work-up needed? Is genetic testing indicated? What is the ideal sample type? How should the patient/family be counselled?

For clinical diagnosis,

-> a number of patient characteristcs are key, including : Ethnic background, Age at presentation (birth/ childhood/ older age), Lesion progression (stable/progressive), Family history (similan lesions, cancers)

-> it is also important to look for associated features : Other skin lesions (freckling, skin tumors...), Dysmophisme, Cardiac disease, endocrine disease ('hyperendocrinopathies), Bony lesions, Eye abdormanlities

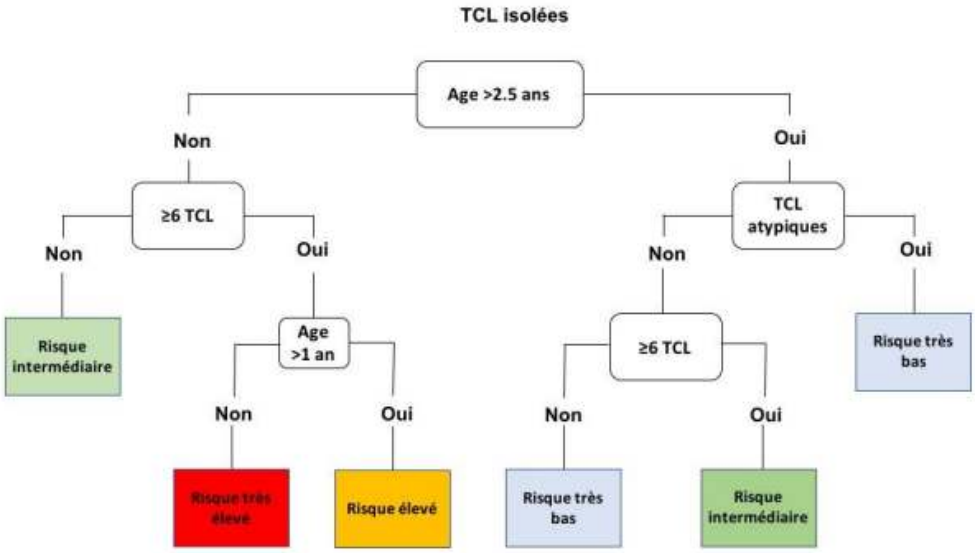
-> collect lesion characteristics are also essential: colour (café-au-lait vs café-noir), size, number, distribution, configuration (typical / atypical / segmental).

Typical CALM

Characteristics: round to oval, tan to brown, flat, hairless, with distinct margins, variable size, and uniform pigmentation.

NF1 risk algorithm (reference: PNDS)

Figure 1 – Algorithme permettant de classifier le risque d'être atteint de NF1, chez les enfants avec des TCL isolées et n'ayant aucun parent atteint de NF1



TCL : Taches café-au-lait

NF1 diagnostic criteria (reference: Legius E et al. Revised diagnostic criteria for neurofibromatosis type 1 and Legius syndrome: an international consensus recommendation. Genet Med. 2021 doi: 10.1038/s41436-021-01170-5. 2021)

Table 1. Revised diagnostic criteria for neurofibromatosis type 1 (NF1).

A: The diagnostic criteria for NF1 are met in an individual who does not have a parent diagnosed with NF1 if two or more of the following are present:

- Six or more café-au-lait macules over 5 mm in greatest diameter in prepubertal individuals and over 15 mm in greatest diameter in postpubertal individuals[a] (Supplementary Fig. 6)
- Freckling in the axillary or inguinal region[a] (Supplementary Fig. 7)
- Two or more neurofibromas of any type *or* one plexiform neurofibroma (Supplementary Fig. 8a, b)
- Optic pathway glioma (Supplementary Fig. 9)
- Two or more iris Lisch nodules identified by slit lamp examination or two or more choroidal abnormalities (CAs)—defined as bright, patchy nodules imaged by optical coherence tomography (OCT)/near-infrared reflectance (NIR) imaging (Supplementary Fig. 10a, b)
- A distinctive osseous lesion such as sphenoid dysplasia,[b] anterolateral bowing of the tibia, or pseudarthrosis of a long bone (Supplementary Fig. 11)
- A heterozygous pathogenic *NF1* variant with a variant allele fraction of 50% in apparently normal tissue such as white blood cells

B: A child of a parent who meets the diagnostic criteria specified in A merits a diagnosis of NF1 if one or more of the criteria in A are present

[a]If only café-au-lait macules and freckling are present, the diagnosis is most likely NF1 but exceptionally the person might have another diagnosis such as Legius syndrome. At least one of the two pigmentary findings (café-au-lait macules or freckling) should be bilateral.
[b]Sphenoid wing dysplasia is not a separate criterion in case of an ipsilateral orbital plexiform neurofibroma.

Atypical CALM :

Criterias for atypical CALMs: Segmental distribution, faint (may fade with time), ethnic variation (especially if <5 macules), no progression.

Atypical CALM+ lentigines

FEATURESS	SYD DE NOONAN	SYD LEOPARD	CARNEY COMPLEX
Primary genes	PTPN11 (50%), SOS1, RAF1, KRAS, BRAF, MAP2K1	PTPN1, RAF1; BRAF	PRKAR1A (70%)
Skin hallmarks	Webbed neck, multiple lentigines, cutis verticis gyrate	Lentigines	Lentigines, blue naevi, myxomas
Pigmentation	CALM	Calms	CALM; periorifical lentigines
Caridac anamalies	Pulmonic stenosis, HCM, coarctation de l'aorta	Pumonic stnosis ECG conduction defects, hypertrophic CM	Myxomas
Dvpt growth	Dvpt delay and short stature	Retarded growth.stature	
others	Cryptorchidism, pectus excavatums, curly hair, distinctive facial gestalt	Abdonaml genitalia, defness, ocular hypertelorism	Pituary adenma, endocrine abdormalitise

Atypical caml + freckling: CMMRD (constitutional mismatch repair deficiency)

Genes: MSH6, MLH1/2, MSH 2

Atypical CALM predominating on trunk and extremities; unilateral axillary freckling in 10–25%; associated hypopigmented patches; pilomatricoma

These patients have a high cancer risk so the diagnosis is important for appropriate management

Segmental CALM

Segmental NF1 (mosaic) carries an unpredictable risk of gonadal involvement so genetic counselling is always difficult. About 30% develop neurofibromas, with a 13% risk of malignancy if neurofibromas are present, and 29% develop symmetric complications.

McCune-Albright syndrome: CALM present at birth, irregular borders, large size, increased melanin production; precocious puberty in ~90%; polyostotic fibrous dysplasia with fracture risk.

Genetic challenges

Molecular testing:

SYNDROME	SPECIMEN	TYPE OF GENETIC TESTINS
NF1, legius, rasopathies	Blood	multigene NGS panel for RASopathy-related genes (*NF1*, *SPRED1*, *PTPN11*, *SOS1*, *BRAF*...); if negative, MLPA for copy-number variants and RNA analysis
Cmmrd	Blood for germline testing Tissue if cancer present	NGS panel (*MLH1*, *MSH2*, *MSH6*, *PMS2*); IHC for loss of MMR protein expression and microsatellite instability testing on tumour tissue
Mc cune albright	Lesional tissue (biopsie)	ultrasensitive droplet digital PCR
PTEN hamartoma syndrome	Priperal blood or tissue	single-gene testing or overgrowth gene panels

Practical tip from the speaker: if initial testing is negative, other testing methods may be tried, so it is important to take enough tissue for two tests at biopsy to avoid running short of usable DNA

DNA repair cancer syndromes

Report written by Dr Lisa Maudet (dermatology, Nancy)

Speaker: Fanny Morice-Picard (France)

Overview of DNA repair disorders

DNA repair relies on a complex and specialized enzymatic pathways, each associated with characteristic clinical syndromes when defective.

- **Base excision repair (BER)** corrects oxidative base damage.
- **Nucleotide excision repair (NER)** corrects bulky DNA lesions, including UV-induced mutations. When the NER system is affected, this can lead to **xeroderma pigmentosum**.
- Homologous recombination (HR) and non-homologous end joining (NHEJ) repair DNA double-strand breaks. When these systems are affected, this can lead to Fanconi anemia, Bloom syndrome, or Rothmund-Thomson syndrome.
- **DNA mismatch repair (MMR)** corrects errors that arise during DNA replication. Defects in this system are observed in **Constitutional Mismatch Repair Deficiency (CMMRD)** and **Muir-Torre syndrome**.

Speaker's note: functional testing of candidate genes should be considered, especially for variants of unknown significance accompanied by suggestive clinical symptoms.

Dermatological manifestations in DNA repair disorders

Skin findings are sometimes the first clinical sign, making their recognition critical for early diagnosis.

Xeroderma pigmentosum is an autosomal recessive disorder linked to defects in NER. It shows genetic heterogeneity, with eight genes associated with different phenotypes.

- **Main clinical features:** skin photosensitivity, which can sometimes be the first symptom, followed by hypo/hyperpigmentation and, in some cases, neurological manifestations.
- **Cancer risk:** patients are at risk of multiple cancers, including early-onset skin cancers (squamous cell carcinoma [SCC], basal cell carcinoma [BCC]) and an increased risk of internal tumors.
- **Treatment considerations:** these patients are highly chemosensitive. Immunotherapy has recently been developed for various skin cancers in this population.
- **Diagnosis:** confirmed by genetic panel testing and a DNA repair assay.

Recent evidence for this disease:

- The implementation of photoprotection measures has decreased the number of skin tumors in these patients, leading to prolonged survival. As a result, it is now becoming apparent that these patients are susceptible to developing internal tumors later in life, notably hematological cancers (associated with the XPC mutation
- *Speaker's note*: Sunburn severity may be linked to DNA repair anomalies via JAK-STAT pathway hyperactivation and an inflammatory cascade, including type I interferon signalling in XPC keratinocytes.

Rothmund-Thomson Syndrome **(Poikiloderma of Rothmund-Thomson)** is an autosomal recessive disease due to a defect in homologous recombination. It shows genetic heterogeneity, with different genes involved (*RECQL4*, *ANAPC1*).

- **Main dermatological features:** skin photosensitivity, possible hypo/hyperpigmentation, and poikiloderma.
- **Extracutaneous features:** cataracts (mainly associated with *ANAPC1* mutations) and skeletal abnormalities.

- **Cancer risk:** patients are at risk of multiple cancers, **primarily early-onset osteosarcoma** (notably with *RECQL4* mutations), with a median age at diagnosis of 11 years. Skin cancers (SCC, BCC) are also frequent but appear later, around age 34. Patients are also at risk of multiple primary tumors, notably lymphoma.
- **Treatment considerations:** these patients are susceptible to chemotherapy, with moderate toxicity.

Bloom syndrome is an autosomal recessive disorder characterized by an increased rate of DNA double-strand breaks. Mutations in the *BLM* helicase gene have been found to cause this disease.

- **Main clinical features:** skin photosensitivity and growth retardation. The syndrome is also associated with immunodeficiency.
- **Diagnosis:** genetic testing for the *BLM* gene and analysis of sister chromatid exchange.
- **Cancer risk:** 29% of cancers occur by age 18, including leukemia, lymphoma, Wilms tumor, osteosarcoma, and medulloblastoma.
- **Treatment considerations:** these patients are extremely sensitive to chemotherapy and require dose adaptation.

Consitutionnal mmmismmatch mmajor deficiency (CMMRD) is an autosomal recessive disease

- **Main dermatological features**: café-au-lait macules (CALM) and NF1-like spots.
- **Cancer risk:** specific tumor phenotypes involving the brain, hematological system, and intestine, with a median age of onset of 6 years.
- **Treatment considerations:** recent studies suggest that high hypermutated tumour burden confers high efficacy with immunotherapy.

Fanconi anemia: Fanconi anemia is an autosomal recessive genetic disease linked to an increased rate of DNA double-strand breaks.

- **Clinical features**: café-au-lait macules and hypopigmentation, as well as extradermatological symptoms (limb malformations, endocrine malformations).
- **Cancer risk**: high risk of myelodysplastic syndrome, as well as an increased risk of skin cancers and other solid tumors.
- **Treatment considerations**: these patients are extremely chemosensitive, and chemotherapy can lead to severe, prolonged, or irreversible myelosuppression. X-rays should also be avoided in these patients.

Speaker note: *why CALM recur across DNA repair disorders:* the *NF1* gene is highly susceptible to post-zygotic (somatic, second-hit) mutations, explaining why CALM are a recurring cutaneous marker across these conditions

Conclusion

Early photoprotection is important given the increased skin cancer risk in these patients. Their impaired DNA repair capacity causes genomic instability and mutation accumulation, conferring strong cancer predisposition and increased sensitivity to radiotherapy and DNA-damaging chemotherapy.

Syndrome	Repair Pathway / Gene(s)	Dermatological Features	Extracutaneous Features	Cancer Risk	Treatment Sensitivity
Xeroderma Pigmentosum	NER; 8 genes (e.g., XPC)	Photosensitivity (often first sign), hypo or hyperpigmentation	Neurological manifestations (variable)	Early-onset SCC/BCC; internal tumors later in life (e.g., hematological, esp. with XPC mutations)	Highly chemo sensitive; responsive to immunotherapy
Rothmund-Thomson Syndrome	Homologous recombination; RECQL4, ANAPC1	Photosensitivity, hypo or hyperpigmentation, poikiloderma	Cataracts (esp. ANAPC1), skeletal abnormalities	Early-onset osteosarcoma; SCC/BCC (-age 34); lymphoma	Moderate chemotherapy toxicity
Bloom Syndrome	BLM helicase (↑ sister chromatid exchange)	Photosensitivity	Growth retardation, immunodeficiency	29% of cancers by age 18: leukemia, lymphoma, Wilms tumor, osteosarcoma, medulloblastoma	Extremely chemo sensitive; requires dose adaptation
CMMRD	Mismatch repair (MMR)	Café-au-lait macules, NF1-like spots		Brain, hematological, and intestinal tumors; median onset age 6	High efficacy with immunotherapy (hypermutated tumors)
Fanconi Anemia	Homologous recombination / DNA crosslink repair (↑ double-strand breaks)	Café-au-lait macules, hypopigmentation	Limb malformations, endocrine malformations	Myelodysplastic syndrome, skin cancers, other solid tumors	Extremely chemo sensitive (severe/irreversible myelosuppression); avoid X-rays

Genetic susceptibility in melanoma

Report written by Dr Lisa Maudet (dermatology, Nancy)

Speaker: Susana Puig (Spain)

Melanoma has strong genetic susceptibility. it is thought to be among the most heritable cancers, with an estimated 60% heritability. This is mainly due to the fact that a number of risk factors for melanoma are actually genetic traits (nevus count, light skin colour, light eye colour, and family history of melanoma)

Multiple genes have been linked to melanoma risk and classified into three categories:

- High risk: CDKN2A, CDK4, BAP1, POT1, TERT, TERF2IP, ACD
- Intermediate risk: MC1R, MITF
- Low risk: ASIP, TYR, TYRP1 and others

CDKN2A

A 2015 meta-analysis (DOI: 10.3978/j.issn.2305-5839.2015.08.11) found *CDKN2A* mutations in ~20% of genetically driven melanoma. CDKN2A is also associated with increased risk of pancreatic, breast, and lung cancer, among others.

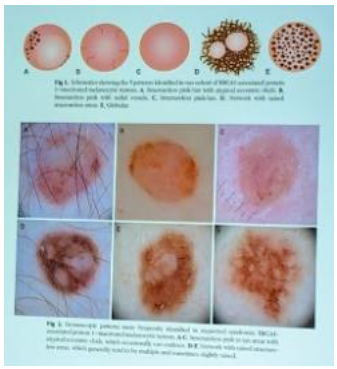
In CDKN2A-mutant families, an earlier age of onset (around the third decade of life), more multiple primary melanomas, more superficial spreading melanoma (SSM) and fewer lentigo maligna melanoma (LMM), and more in-situ/thinner melanomas were observed. CDKN2A families also tended to have brown-olive skin phototype and a less frequent history of sunburn.

In *CDKN2A* melanoma families, individuals who develop melanoma without carrying the family's CDKN2A mutation are termed phenocopies. This means that there is no identified genetic variant, but presumably linked to shared environmental/lifestyle exposure within the family.

Given the risk of developing melanoma and pancreatic cancer, specific surveillance is proposed to allow early detection and adapted management; no precursor lesion for pancreatic cancer has been identified to date.

Other genes

BAP 1



BAP1 is the only known gene associated with risk of both cutaneous melanoma and uveal melanoma. It is also associated with risk of other cancers (BCC, mesothelioma, renal cell carcinoma). BAP1-inactivated nevi are characteristic, reflecting loss of BAP1 expression and consequent loss of pigmentation in parts of the lesion.

Telomere genes (POT1, TERT)

Families with longer telomeres carry a higher risk of melanoma, notably of aggressive and spitzoid subtypes, with a substantial associated risk of sarcoma; the speaker proposed specific surveillance protocols for early detection in these families, as well as being extremely carefull for anu nez lesion identified on those patients.

MC1R

MC1R is the main gene responsible for the red-hair phenotype. Polymorphisms in this gene are associated with increased risk of melanoma and non-melanoma skin cancer, as well as an earlier age of onset. High nevus count and MC1R red-hair variants act synergistically to increase melanoma risk.

MITF E318K

The MITF E318K variant is associated with a markedly higher nevus count (mean ~84 vs 32 in non-carriers), a more reticulated nevus pattern, and more frequent nodular melanoma (OR 4.48).

Follow-up of high-risk patients

For melanoma, a two-step follow-up combining **total body photography** and **dermoscopy** is recommended. Some centers have added confocal microscopy to increase specificity. This surveillance approach has highlighted specific patterns of nevus distribution, with genotype–dermatological phenotype correlations described for *CDKN2A*, *POT1*, *POLE*, and *BAP1* variant carriers (https://doi.org/10.1093/bjd/ljag137) — raising hope that nevus distribution patterns could eventually help predict the underlying mutation.

Surveillance for other associated cancers:

- Pancreatic cancer: CDKN2A, BAP1
- Breast cancer: CDKN2A, BAP1, BRCA1/2, ATM, TP53
- Renal cancer: BAP1, MITF
- Other skin cancer: BAP1, MC1R

Indications for gentic testing

Criteria vary internationally:

- US, UK, Europe: ≥3 melanomas in first/second-degree relatives, or 2 melanomas + 1 pancreatic cancer
- Australia: ≥4 melanomas in first/second-degree relatives, or 3 melanomas + 1 pancreatic cancer
- Latin America and Spain: 2 melanomas, or 1 melanoma + 1 pancreatic cancer

In Spain, the probability of finding a mutation under these criteria is close to 1%.

In conclusion

CDKN2A mutations are associated with atypical nevi and risk of melanoma, uveal melanoma, and other cancers.

Telomere genes increase the risk of melanoma and uveal melanoma, as well as melanoma-related mortality, spitzoid morphology, and large nevi.

MITF mutations are associated with numerous reticulated nevi and risk of melanoma, uveal melanoma, and fast-growing melanoma.

Deep phenotyping with AI algorithms will likely help characterize patients and may eventually help predict genetic background and, more importantly, the risk of developing melanoma and other cancers. Identifying at-risk individuals allows implementation of primary and secondary prevention with appropriate management.

Genetic predisposition to cutaneous squamous cell and basocellular carcinomas

Report written by Dr Lisa Maudet (dermatology, Nancy)

Speaker: Sarah Guégan (France)

Gorlin syndrome

Diagnostic criteria: Diagnostic rule: 1 major criterion + molecular confirmation OR 2 major criteria + 1 minor criterion OR 1 major criterion + 3 minor criteria (Reference: Bree et al., Am J Med Genet A, 2011)

MAJOR CRITERIA	MINOR CRITERIA
BCC (basal cell carcinoma) > 1, or 1 BCC before age 20	Rib abnormalities
Odontogenic cysts before age 20	Other skeletal malformations (spinal abnormalities, kyphoscoliosis, polydactyly)
Palmar-plantar pits	Macrocephaly, frontal bossing, hypertelorism
Calcification of the falx cerebri	Cleft palate
Medulloblastoma	Cardiac or ovarian fibroma
First-degree relative with Gorlin syndrome	Mesenteric cyst
	Ocular abnormalities (strabismus, hypertelorism, congenital cataract, glaucoma, coloboma)

Germline pathogenic variants: *PTCH1*, *SUFU* leading to an activation of the Sonic Hedgehog signalling pathway

- Autosomal dominant inheritance
- 30% of cases are de novo

Bazex-Dupré-Christol syndrome

Clinical manifestations include multiple BCCs (in sun-exposed areas) from the age of 3 with 50% of cases before the age of 20 as well as other characteristic features: hypotrichosis, facial hyperpigmentation, facial milia, follicular atrophoderma on the dorsal hands

Germline pathogenic variants: mutation *ACTRT1*

- Clinique: hypotrichoses, hyperpigmentation of the face, milia on th efface, follicular atrophoderma of the back of the hands
- Multpls cbc from

Other syndromes

Ferguson-Smith syndrome:

- Clinical manifestation: Multiple, self-involuting keratoacanthomas; first lesion between ages 20–70, developing over 3–4 weeks in sun-exposed areas, with spontaneous involution within 3–6 months
- Genetic testing: Loss-of-function mutation in TGFBR1, autosomal dominant with high penetrance (germline mutation + second hit mechanism)

Lynch syndrome (Muir-Torre phenotype):

- Skin tumor predisposition:
    - sebaceous tumors from the age of 20, with an average age at onset of 53 years; these include both benign lesions (sebaceous adenoma) and malignant tumors (sebaceous carcinoma, sebaceous-differentiated basal cell carcinoma).
    - Basal cell carcinomas as well as cutaneous squamous cell carcinomas and keratoacanthomas.
- *Genetic testing*: The syndrome is caused by germline pathogenic variants in MLH1, MSH2, MSH6, PMS2, or EPCAM, with autosomal dominant inheritance and high penetrance following a second-hit mechanism; MSH2 mutations account for 90% of cases. Tumorigenesis follows a germline mutation combined with loss of heterozygosity within the tumors.

Epidermodysplasia verruciformis

- *Skin tumor predisposition*: multiple cutaneous squamous cell carcinomas driven by beta-HPV infection (HPV5 or HPV8). Syndromic forms have also been described in association with other genes, including RHOH, CORO1A, DOCK8, LCK, TPP2, STK4, and ITK.

The lifetime risk of progression to squamous cell carcinoma ranges from 30 to 70%, occurring particularly in sun-exposed areas, which underlines the importance of sun protection in these patients.

- *Genetic testing*: autosomal recessive genodermatosis caused by a germline mutation in TMC6/EVER1 or TMC8/EVER2, or in CIB1.

Incontinentia pigmenti:

- *Skin features* : Cutaneously, it presents with linear vesicular lesions following Blaschko's lines, which progress successively through a verrucous stage, a pigmented stage, and finally an atrophic stage; multiple subungual keratoacanthomas may also be observed.
- *Extracutaneous features* include dental anomalies (missing or conical teeth), ocular abnormalities (retinal anomalies), and CNS involvement (seizures, developmental delay).
- *Genetic testing*: genodermatosis with X-linked dominant inheritance that is lethal in utero in hemizygous males, and therefore affects girls almost exclusively. It is caused by a germline mutation in IKBKG (NEMO).

Management of patients with skin cancer

For basal cell carcinoma (BCC), oral targeted therapy with Hedgehog (SHH) pathway inhibitors is available for advanced disease. These agents are associated with a substantial burden of adverse events (notably dysgeusia), which can be mitigated through intermittent dosing strategies, such as on-off treatment schedules or alternative regimens (e.g. treatment every other day, or on 5 days per week rather than continuously).

For squamous cell carcinoma (SCC), immunotherapy has revolutionized tumor management, supported by results from five major trials. A real-life prospective study of neoadjuvant cemiplimab in advanced cutaneous SCC showed a low grade of toxicity, with grade ≥3 adverse events occurring in 18% of patients.

Adjuvant cemiplimab after surgery, with or without radiotherapy, in cutaneous SCC has also shown promising results, with a significant prolongation of disease-free survival.

Take homme message

- Prevention of skin cancer is key in patients at risk due to a genetic condition
- Life long dermatologic surveillance needed
- Early management of skin cancer with surgical excision or topical therapy when possible
- Targeted therapies and immunotherapy have transformed the prognosis of advanced carcinomas and are now used in neoadjuvant and adjuvant settings