Recognizing skin manifestations of hematologic diseases is important for the:

- Early diagnosis of hematologic neoplasms/relapses
- Prognosis of the disease
Skin manifestations of hematooncologic disorders can be classified as:

1. **Specific lesions** (excluding primary cutaneous lymphomas)

2. **Associated / paraneoplastic lesions**

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**Introduction**

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**1. Specific skin lesions**

= *Leukaemia cutis* --> skin lesions due to infiltration of leukemic cells

1. **Myeloid leukaemia cutis**
   - mainly AML M4/5 (>50% of cases)
   - less frequently: AML M1/3, CML, myelodysplastic disorders
     - Worsening of the prognosis
     - Leukemia cutis may be first symptom in ~ 5 % of AML patients
     - therapeutic challenge!

2. **Lymphoid leukaemia cutis**
   - mainly CLL, rarely ALL
   - Papules, plaques, tumors, sometimes hemorrhagic
Specific lesions in myeloid hemopathies

- Hyperplasia of oral mucosa
- In AML, oral cavity is frequently early involved
  - 80% of AML patients (M4, M5)
- Often the first symptom of disease!

Chronic myelomonocytic leukemia
Specific lesions in myeloid hemopathies

Plasmacytoid dendritic cell neoplasm

CD123
Myeloid haemopathies: 
*atypical specific skin lesions*

- Difficult to diagnose (histology)
- More abundant in myelodysplastic syndrome 
  (frequently a sign of transformation in acute leukemia)
  - blisters
  - necrotic lesions
  - subcutaneous nodules
  - prurigo
  - ecchymoses

Histologic and Immunohistologic Characterization of Skin Localization of Myeloid Disorders. A Study of 173 Cases

C Bénet, A Gomez, C Aguilar, C Delattre, B Vergier, M Beylot-Barry, S Fraitag, A Carlotti, P Dechelotte, V Hospital, M d’Incan, V Costes, O Dereure, N Ortonne, M Bagot, L Laroche, A Blom, S Dalac, and T Petrella
Specific skin lesions in lymphoid hemopathies

Types:

- Angioimmunoblastic T-cell lymphoma
  (Angioimmunoblastic lymphadenopathy with dysproteinemia; AILD)

- HTLV-1 Leukemic Lymphoma

- CLL: Specific and insect-bite like reactions

- Intravascular B-cell lymphoma
1. **Angioimmunoblastic T-cell Lymphoma**

(Angioimmunoblastic Lymphadenopathy with Dysproteinemia: AILD)

- Febrile, maculo-papular eruption
  (DD: adverse cutaneous drug eruption)

- Lymphadenopathy, polyclonal hypergammaglobulinemia, hepatosplenomegaly

- Skin lesions in 40% of cases

- Precedes diagnosis of the hemopathy in 30% of cases
1. Angioimmunoblastic T-cell Lymphoma

IgA linear dermatosis
2. Leukemic HTLV-1 Lymphoma:

- Adult T cell leukemia/lymphoma (ATLL)
- 60% of cases --> skin involvement
- Diffuse red-brown papulo-nodular skin eruption
- Erythroderma possible

3. Chronic lymphocytic leukemia
3. Chronic lymphocytic leukemia

Insect-like bite reactions

4. Intravascular B-cell lymphoma
Plan

Skin manifestations of haematooenctologic disorders can be classified as:

1. **Specific lesions** (excluding primary cutaneous lymphomas)

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### Associated/paraneoplastic skin lesions

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</table>
1. Neutrophilic Dermatoses: Sweet-Syndrome

- 8-13% of Sweet-Syndrome cases associated with a hemopathy
- 11% of cases precede the diagnose of the hemopathy
- Usual clinical presentation but:
  - More often bullous (75% of cases)
  - More often on arms (94% of cases)

**Clinical signs:**
- Livid red papules-nodules
- Irregular surface (mountainous..)
- Fever > 38°C, elevated CRP
- Leucocytosis with neutrophilia (> 70%)

1. Neutrophilic Dermatoses: Pyoderma gangrenosum

- Associated with: Myeloma (IgA), Myeloid Leukemias, Polyglobuly, Thrombocytosis, Myelofibrosis
- No specific clinical presentation
  (Bullous variant more frequent?)
- Disseminated form often associated with IgA Paraproteinemia

**Clinical signs:**
- Centrifugally developing painful and necrotic ulcer(s)
- Livid red and undermined border
1. Neutrophilic Dermatoses: *Erythema elevatum et diutinum*

**Associated with:**
- Myeloid hemopathies in 46% of cases
- Also often with IgA Myeloma

**Clinical signs:**
- Bright-livid red papules, nodules, plaques
- Flat surface, depressed center
- Disseminated or aggregated
- Extensor surfaces of extremities (feet, knees, hands)

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1. Neutrophilic Dermatoses: *Sneddon-Wilkinson-Syndrome*

- Pustulosis subcornealis
- In contrast to other neutrophilic dermatoses
  - connection with lymphoid disorders
  - frequently IgA Gammopathies (benign/MM)

**Clinical signs:**
- Superficial small-large pustules with inflammatory borders
- Circinar-polycyclic erosions, collerette scales
- Symmetric on trunk, proximal extremities, body folds
1. Neutrophilic Dermatoses:  

**Neutrophilic eccrine hidradenitis**

- Almost exclusively associated with AML
- Development frequent during post-chemotherapy aplasia  
  ( Anthracycline, Cytarabine, Cyclophosphamide, Sorafenib, Imatinib)
- Rarely precedes hematologic disorders

**Clinical signs:**
- Similar to Sweet syndrome, but location on eccrine sweat gland areas,
- Painful papules and nodules, plaques
- Palmoplantar, axilla, extremities, face/neck (peri orbital)

**Associated/paraneoplastic skin lesions**

| 1. Neutrophilic dermatoses | Sweet-Syndrom  
|                           | Pyoderma gangraenosum  
|                           | Erythema elevatum et diutinum  
|                           | Sneddon-Wilkinson Syndrome  
|                           | Neutrophilic eccrineHidradenitis |

| 2. Vascular manifestation | Livedo  
|                          | Erythromelalgia  
|                          | Vasculitis  
|                          | Superficial Phlebitis  
|                          | Cryoglobulaemia  
|                          | Myelodyplasia, M. Waldenström  
|                          | Myelodyplasia, CML  
|                          | Myelodyplasia, hairy cell leukemia  
|                          | Acute leukemia (Adenocarcinoma)  
|                          | Multiple Myeloma, M. Waldenström |

| 3. Lesions via Ig deposition | Amyloidosis  
|                            | Macroglobulinaemia (M. Waldenström)  
|                            | Acral follicular hyperkeratosis |

| 4. Lesions via mAb Activity of Ig | Necrobiosis Xanthogranuloma  
|                                   | Xanthoma planum  
|                                   | Schnitzler syndrome  
|                                   | Paraneoplastic Pemphigus |

| 5. Varia | Scleromyxedema  
|          | Urticaria  
|          | Pruritus/Prurigo  
|          | Erythema nodosum  
|          | POEMS Syndrome |
2. Vascular manifestations:

Mainly in myeloid hemopathies (myelodysplasia)

- **Livedo:** Polycythemia, Thrombocythemia, Waldenströms disease

- **Erythromelalgry:** Polycythemia (30%), Thrombocythemia, CML

Clinical signs:
- Increased sensitivity towards heat
- Hyperaemia, erythema, swelling
- Burning sensation
- Increased skin temperature
- Hyperhidrosis (or Hypo-/Anhidrosis)

• **Vasculitis:** rare

- 2 Types:
  - Infiltrated purpura (Histo: leucocytoclastic vasculitis)
  - Periarteritis Nodosa-like nodular subcutaneous skin lesions (Histo: granulomatous vasculitis)

- Appear often before the diagnosis of hemopathy
  - Tricholeucocytic leukemia
  - Myelodysplastic syndrome

- Drug or Infections (Mycobacteria) in immunosuppressed patients may be a confounding factor
2. Vascular manifestations:

- **Superficial phlebitis**: in 6% of polyglobuly patients
- **Cryoglobulinemia:**
  - **Type I:**
    - Monoclonal (usually IgG or IgM)
  - Association with B-cell proliferations
    - Myeloma
    - Waldenström

Clinic: acrocyanosis, vascular occlusion + ulcer(s), purpura induced by cold, ecchymosis, acral hyperpigmentation

## Associated/paraneoplastic skin lesions

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|-----------------------------|------------------------------------------|
| 2. Vascular manifestation    | Livedo  
Erythromelalgie  
Vasculitis  
Superficial Phlebitis  
Cryoglobulinaemia |
| 3. Lesions via Immunoglobulin deposition | Amyloidosis  
Macroglobulinaemia  
Acral follicular hyperkeratosis |
|                            | Multiple Myeloma, M. Waldenström  
M. Waldenström  
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| 5. Varia                   | Scleromyxedema  
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POEMS Syndrome |
3. Lesions due to Ig deposition:

Associated with B-cell hemopathies

a. Amyloidosis: most frequent

- AL Type systemic amyloidosis
- Clinical signs:
  - Purpura (face-eyelids, folds)
  - Macroglossia (painful)
  - Papules-nodules (whitish or yellowish)
- Histo: Dermal amyloid deposits

b. Macroglobulinemia:

- In Waldenström’s disease
  (Plasmocyte proliferation with monoclonal IgM production)
- Clinic:
  - Mucosal bleeding (mouth/nose), CNS, retina..
  - Characteristic symmetrical pink papules/nodules often with petechiae --> face, ears

c. Acral follicular spicules:

- IgG deposits in follicular ostium of myeloma patients
## Associated/paraneoplastic skin lesions

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- Sweet-Syndrom
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- Neutrophilic eccrineHidradenitis

### 2. Vascular manifestation
- Livedo
- Erythromelalgia
- Vasculitis
- Superficial Phlebitis
- Cryoglobulinaemia

### 3. Lesions via Ig deposition
- Amyloidosis
- Macroglobulinaemia (M. Waldenström)
- Acral follicular spicules

### 4. Lesions via mAb Activity of Immunoglobulins
<table>
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### 5. Varia
- Scleromyxedema
- Urticaria
- Pruritus/Prurigo
- Erythema nodosum
- POEMS Syndrome

## 4. Lesions caused by mAb activity of Ig

- **a. Necrobiotic xanthogranuloma**
  - Rare disease
  - 90% of cases associated with monoclonal IgG κ oder λ paraprotein, 40% cryoglobulinemia

**Clinical signs:**
- Red-orange to violet papules --> sharply delimited plaques with xanthomatous aspect
- Frequent central ulceration or atrophy with telangiectasias
- Localisation: 85% periorbital, also trunk, extremities, mouth
4. Lesions caused by mAb activity of Ig

a. Necrobiotic xanthogranuloma

- Pathogenesis and treatment of xanthomatosis associated with monoclonal gammopathy
  
  Blood 2011 Oct 6;118(14):3777-84

b. Xanthoma planum

- Multiple myeloma: monoclonal Ig-lipoprotein complex
- Tissue deposition and consecutive macrophage activation

c. Schnitzler syndrome

- Urticaria, fixed, little pruritus
- Arthralgias & bone pain
- Recurrent fever bouts
- Monoclonal IgM
- Interleukin 1β activity,
  therapy: Anakinra (IL1Ra-Fc)
4. Lesions caused by mAb activity of Ig

d. Paraneoplastic pemphigus
PNP pemphigus due to NK/T cell lymphoma, Br J Haematol 2011

4. Lesions caused by mAb activity of Ig

e. Generalized acquired cutis laxa
- Myeloma
- Granuloma annulare plaque
- Immunologic destruction of elastic fibers

Douglas New, Arch Dermatol 2011
Associated/paraneoplastic skin lesions

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   - Sweet-Syndrom
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   - Sneddon-Wilkinson Syndrom
   - Neutrophilic eccrineHidradenitis

2. Vascular manifestation
   - Livedo
   - Erythromelalgia
   - Vasculitis
   - Superficial Phlebitis
   - Cryoglobulinaemia

3. Lesions via Ig deposition
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   - Macroglobulinaemia (M. Waldenström)
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4. Lesions via mAb Activity of Ig
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   - Paraneoplastic Pemphigus

5. Varia
   - Scleromyxedema
   - Urticaria
   - Pruritus/Prurigo
   - Erythema nodosum
   - POEMS Syndrome
   - Multiple Myeloma
   - various
   - M. Hodgkin, various
   - M. Hodgkin
   - Multiple myeloma

5. Varia:

   **Scleromyxedema**

   - Most cases associated with monoclonal IgG paraproteinaemia of the \( \lambda \) light chain type
   - Association with multiple myeloma or Waldenström

   **Clinical signs:**
   - Upper thoracic area with thickened skin
   - Solitary solid skin-coloured papules → neck & frontal regions
   - Reduced mobility (sclerodermiform)
5. Varia: Scleromyxedema
5. Varia:  
**Scleromyxedema**

- Polyneuropathy *(peripheral sensomotoric disturbances)*
- Organomegaly *(Hepatosplenomegaly, Lymphadenopathy)*
- Endocrinopathy
- Monoclonal Gammopathy

**Skin Alteration:**
- Hyperpigmentation (77%)
- Sclerodermiform alterations (60%)
- Hypertrichosis (50%)
- Haemangioma *(Histo: glomeruloid)*
- Leukonychia (20%)

+ overproduction of IL 1, IL 6, TNF
Summary

There are specific and associated skin signs of haematooncologic disorders.

We have to recognize them, as they

- May allow earlier diagnosis and better treatment
- Can be predictive for prognosis

Dermatological exam and Biopsy