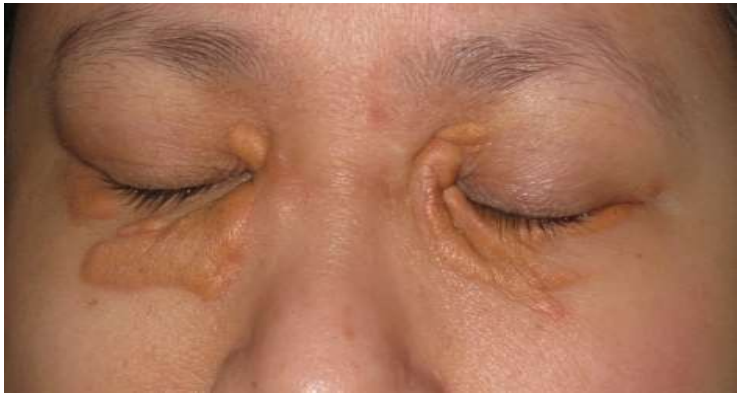
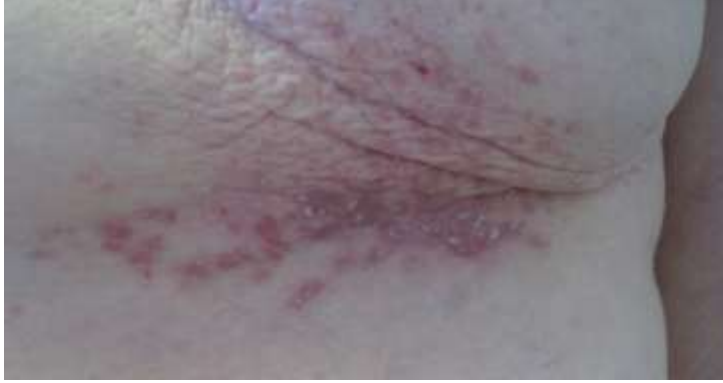




Manifestations cutanées des histiocytoses (groupe L)

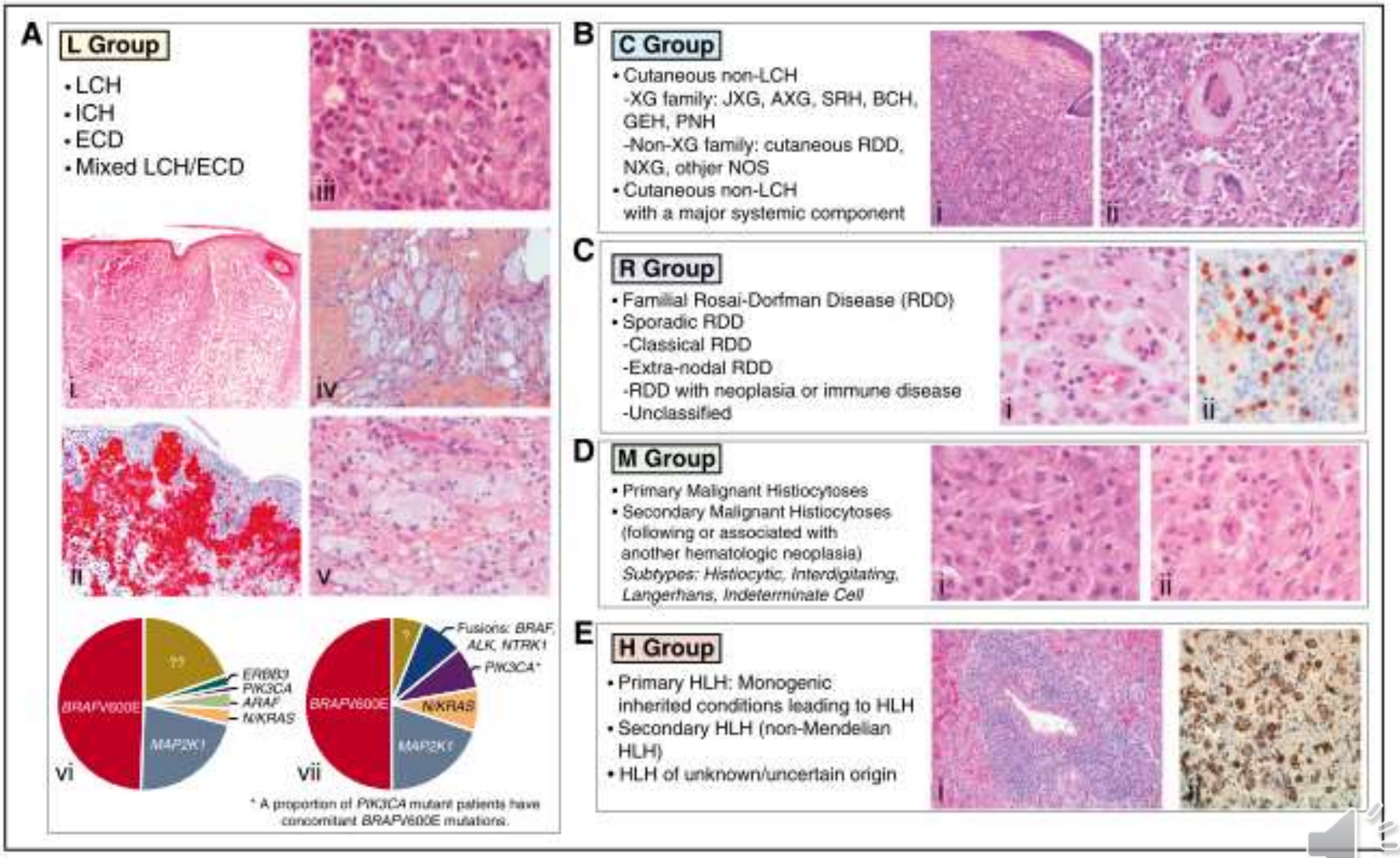
François CHASSET

MCU-PH

Service de dermatologie et allergologie
hôpital Tenon

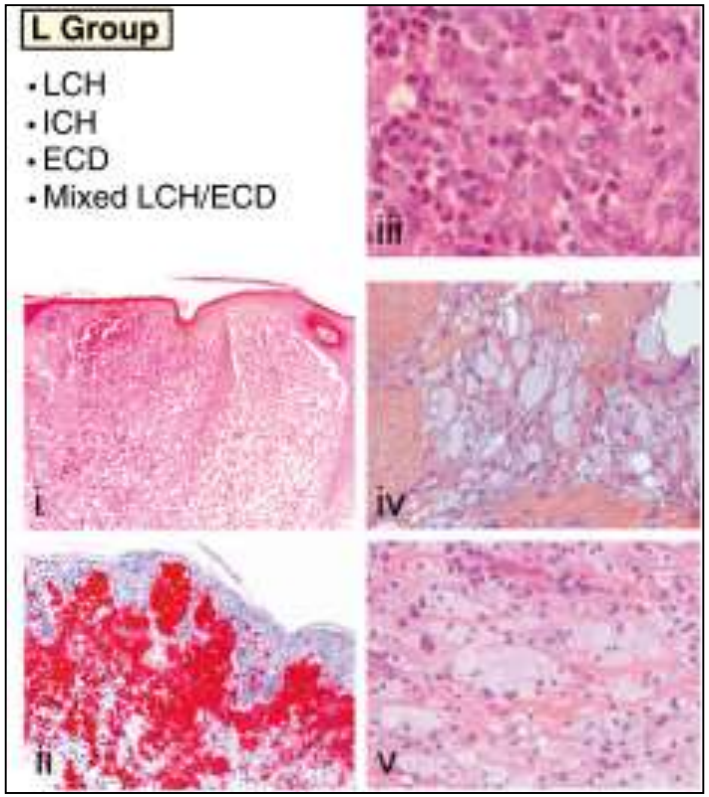
francois.chasset@aphp.fr

Classification des histiocytoses



Emile, Blood 2016

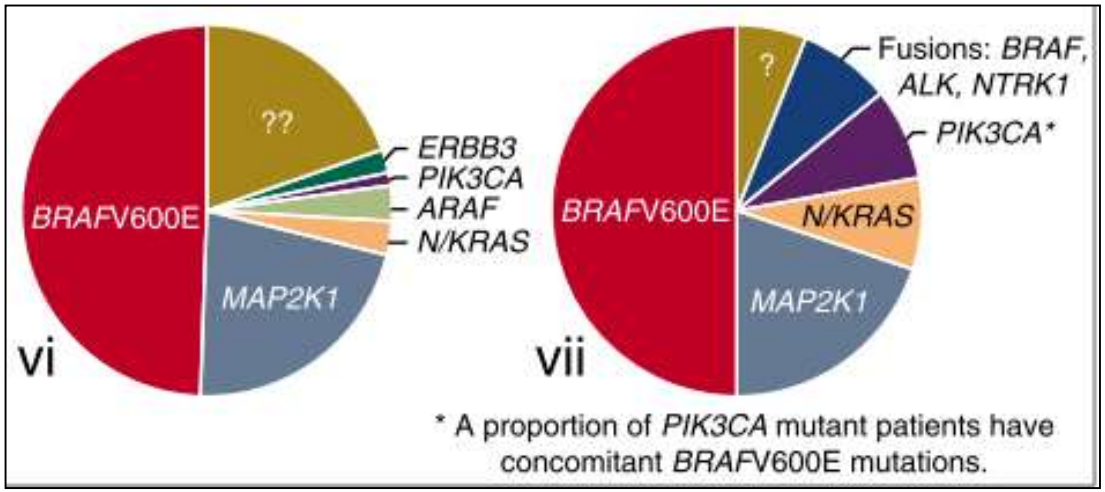
Histiocytoses du groupe L



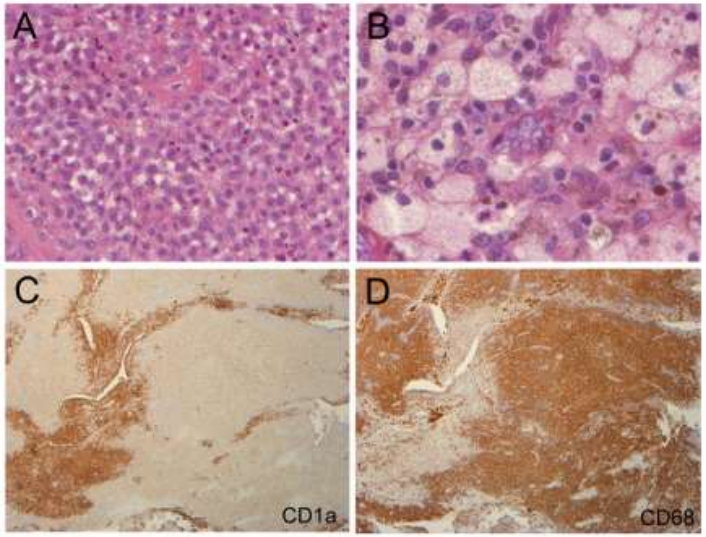
- Histiocytose Langerhansienne
- Maladie d'Erdheim-Chester
- Histiocytose mixte
- Histiocytose indéterminée

Emile, Blood 2016

Rationnel du regroupement des histiocytoses du groupe L



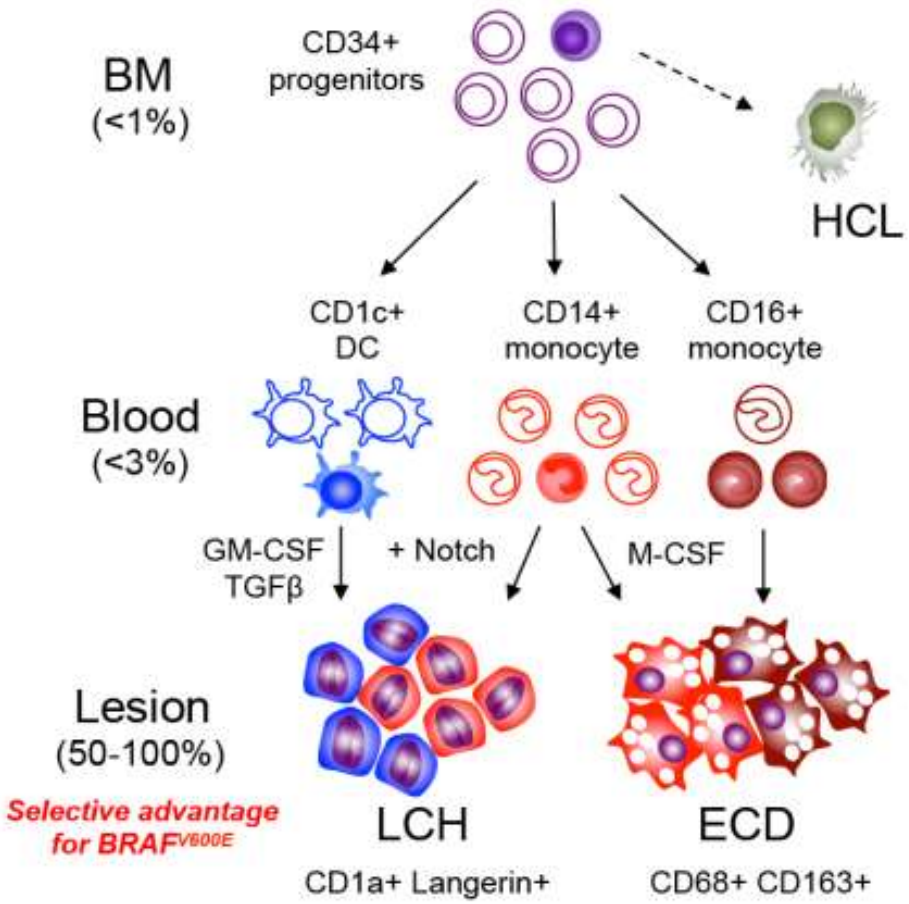
Activation dans les deux pathologies de mutations activatrices de la voie MAPK



Présence de composant de LCH et d'ECD au sein de la même biopsie dans plusieurs cas d'histiocytoses mixtes

Emile, Blood 2016; Hervier Blood 2014

Origine des histiocytes « pathologiques » dans les histiocytoses du groupes L



Leucémie à tricholeucocytes

Survenue de la mutation BRAF à différents moments de la maturation expliquant les différents phénotypes

Milne, Blood 2017

Histiocytoses du groupe L

Table 1. Histiocytoses of the L group

Disease	Subtypes
LCH	LCH SS
	LCH lung^{+}
	LCH MS-RO^{+}
	LCH MS-RO^{-}
	Associated with another myeloproliferative/ myelodysplastic disorder
ICH	
ECD	ECD classical type
	ECD without bone involvement
	Associated with another myeloproliferative/ myelodysplastic disorder
	Extracutaneous or disseminated JXG with MAPK-activating mutation or ALK translocations
Mixed ECD and LCH	

RO : risk organs

Emile, Blood 2016

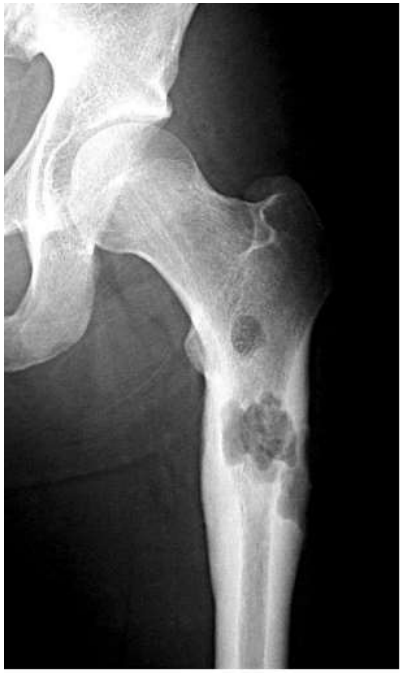
Histiocytoses Langerhansiennes

- Plusieurs formes :
  - Pédiatriques +++
  - Adultes
  - Atteinte mono-organe: os, peau, ganglionnaire
    - Granulome à éosinophile limité à l'os
    - Forme aigue cutanée aigüe, autorésolutive de Hashimoto Prisker
  - Atteinte pulmonaire + fréquente chez adulte
  - Atteinte multi-organe sans atteinte organe à risque
    - Hand Shuller Christian
  - Atteinte multi-organe avec atteinte organe à risque
    - Letterer-Siwe
    - Organes à risque: Foie, rate, médullaire

Histiocytoses Langerhansiennes

- Plusieurs formes :
  - Pédiatriques
  - Adultes
  - Atteinte mono-organe: os, peau, ganglionnaire
    - ~~Granulome à éosinophile limité à l'os~~
    - ~~Forme aigue cutanée aigüe, autorésolutive de Hashimoto Prisker~~
  - Atteinte pulmonaire + fréquente chez adulte
  - Atteinte multi-organe sans atteinte organe à risque
    - ~~Hand Shuller Christian~~
  - Atteinte multi-organe avec atteinte organe à risque
    - ~~Letterer-Siwe~~
    - Organes à risque: Foie, rate, médullaire

Histiocytoses Langerhansiennes



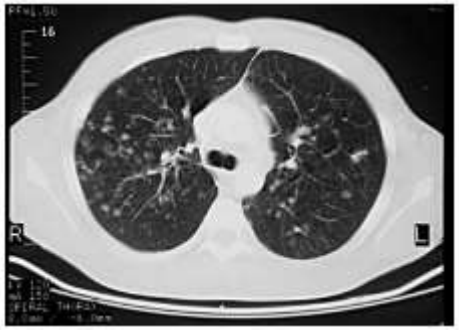
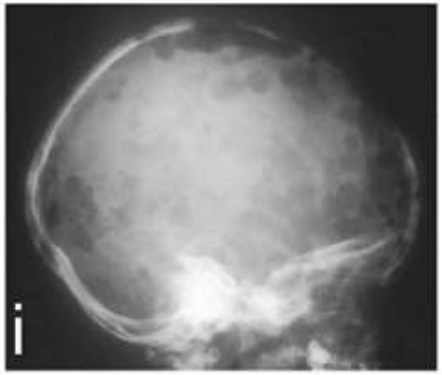
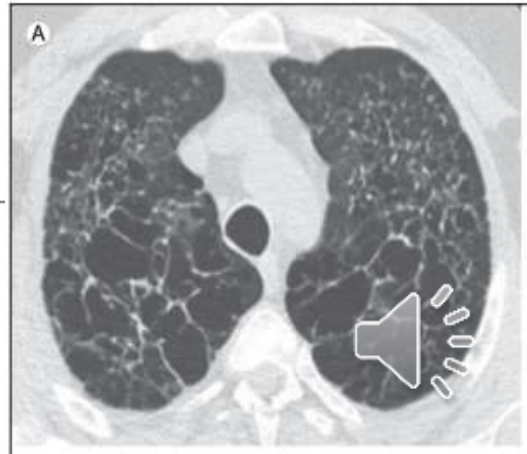


Table 2. Diagnostic work-up of patients suffering from adult LCH

Diagnostic work-up	Procedure
Baseline evaluation	Bone scan, chest X-ray, skeletal X-ray, abdominal ultrasound, routine laboratory
Additional diagnostic procedures	
Pulmonary involvement	High-resolution computed tomography, pulmonary function tests including DCLO, bronchoalveolar lavage
Bone involvement	Computed tomography, magnetic resonance imaging
Pituitary gland involvement	Hormone analysis, cranial computed tomography, magnetic resonance imaging
Skin involvement	Skin biopsy
Gastrointestinal invovlvemet	Endoscopy
Visceral organ involvement	Computed tomography
Bone marrow involvement	Marrow biopsy
Genitourinary tract involvement	Gynaecological examination





Atteinte machoire +++ 30%

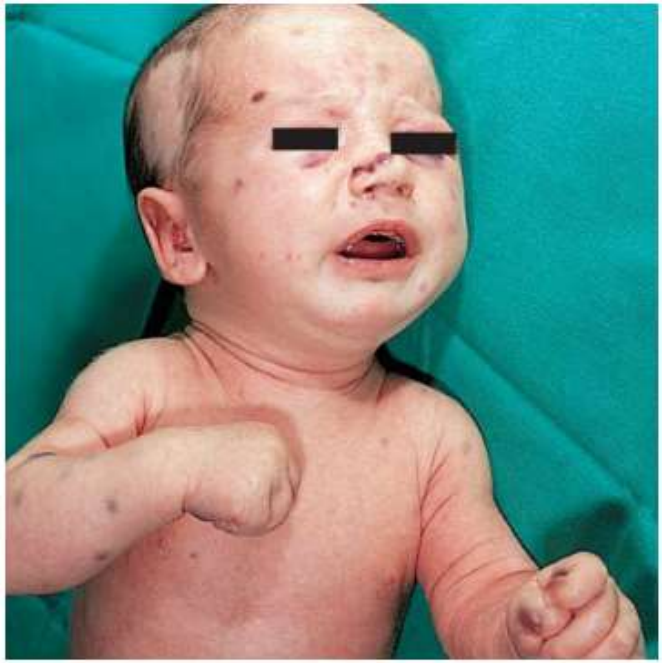
Emile, Blood 2016, Haroche Lancet oncol 2017

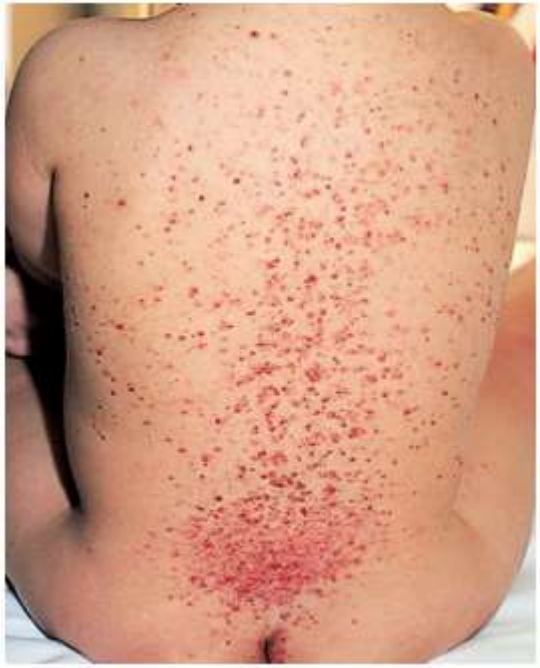
Histiocytose Langerhansienne

Lésions cutanées chez 1/3 des patients:

- Souvent polymorphes
- Papulo-crouteuses +++
- Intertrigos +++
- Atteinte cuir chevelu +++
- Parfois lésions pustuleuses
- Evolution purpurique
- Formes localisées versus diffuses

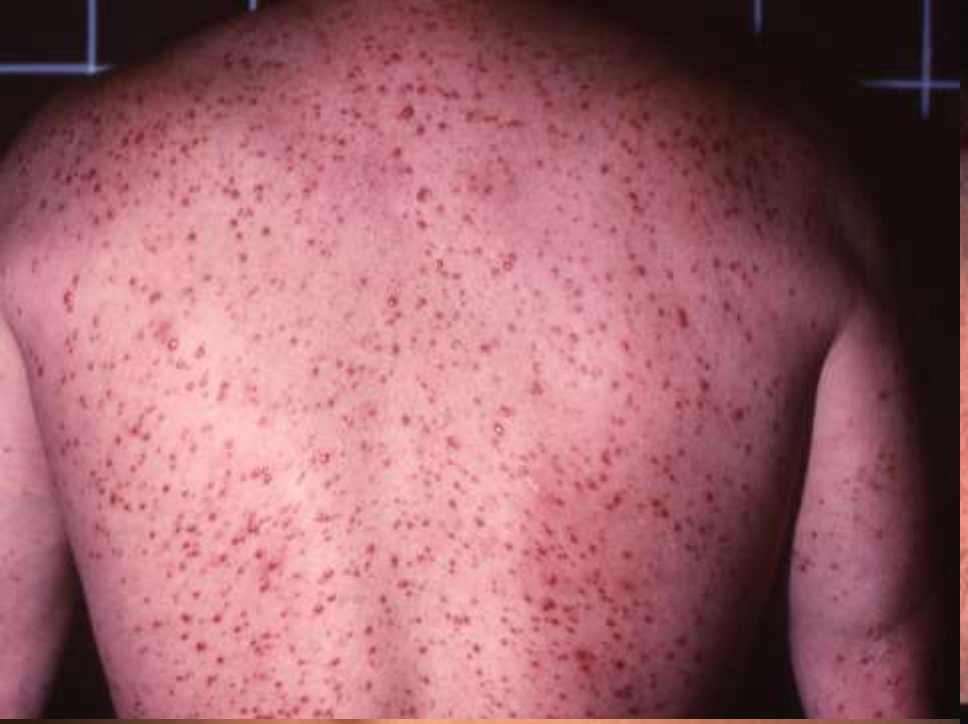
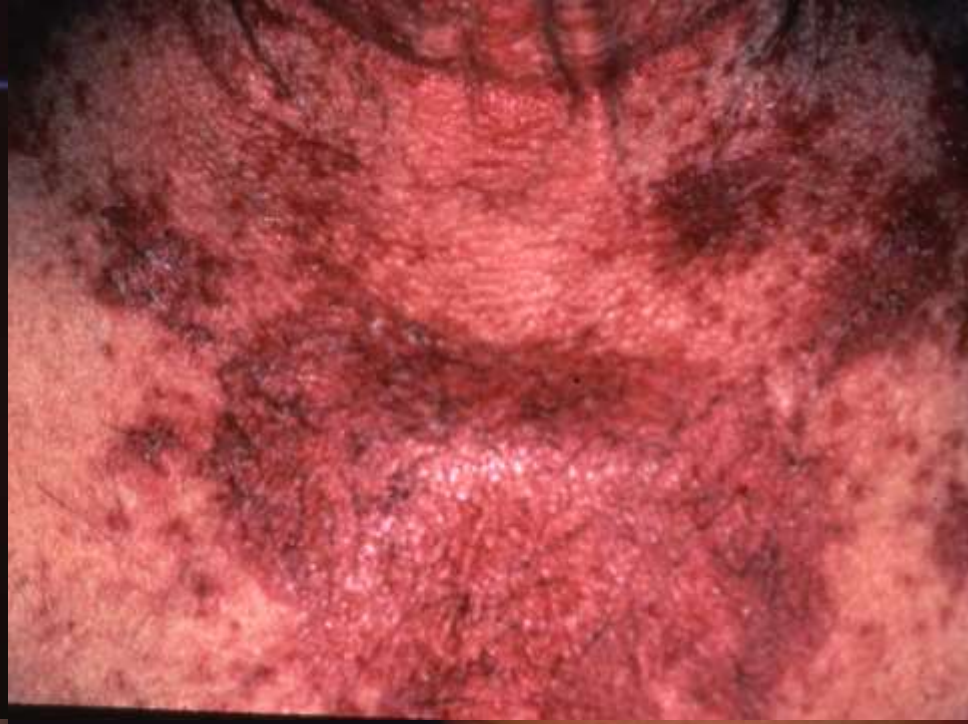
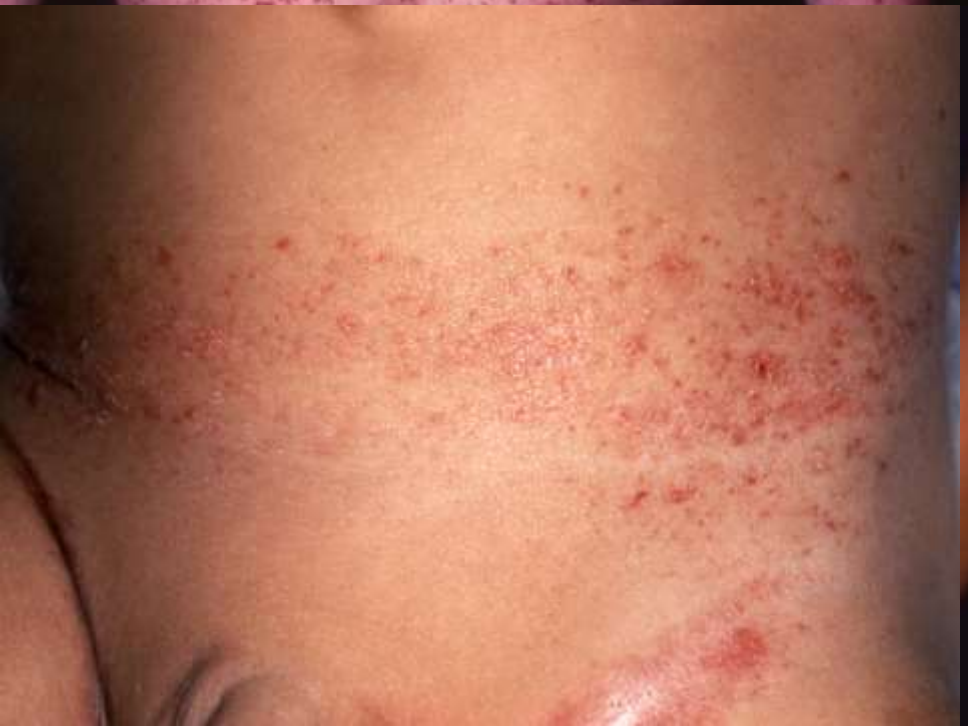
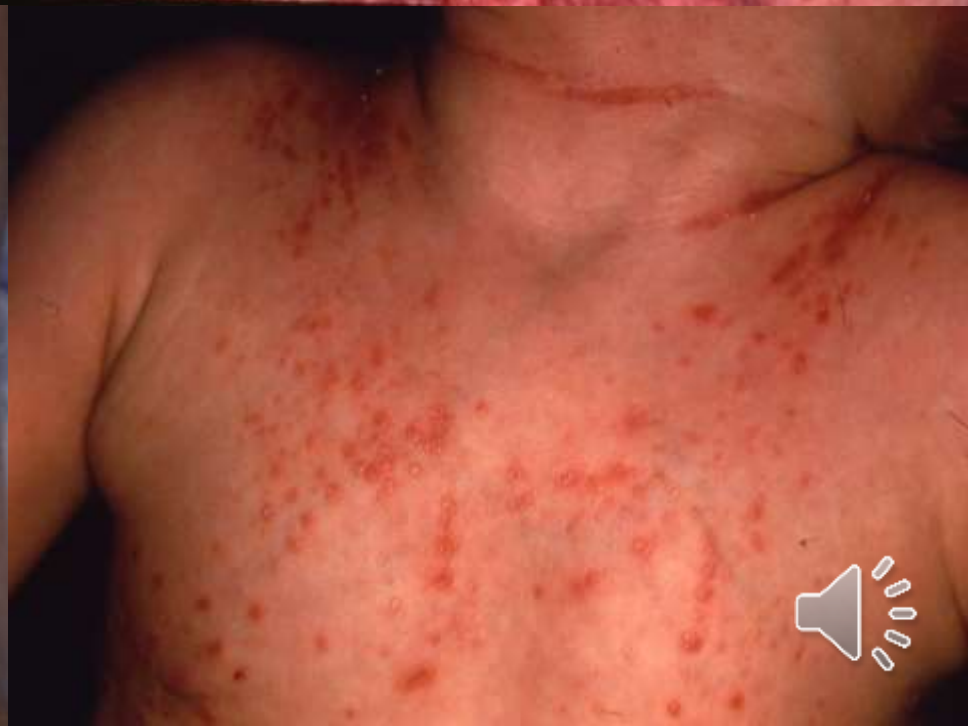
Histiocytose Langerhansienne

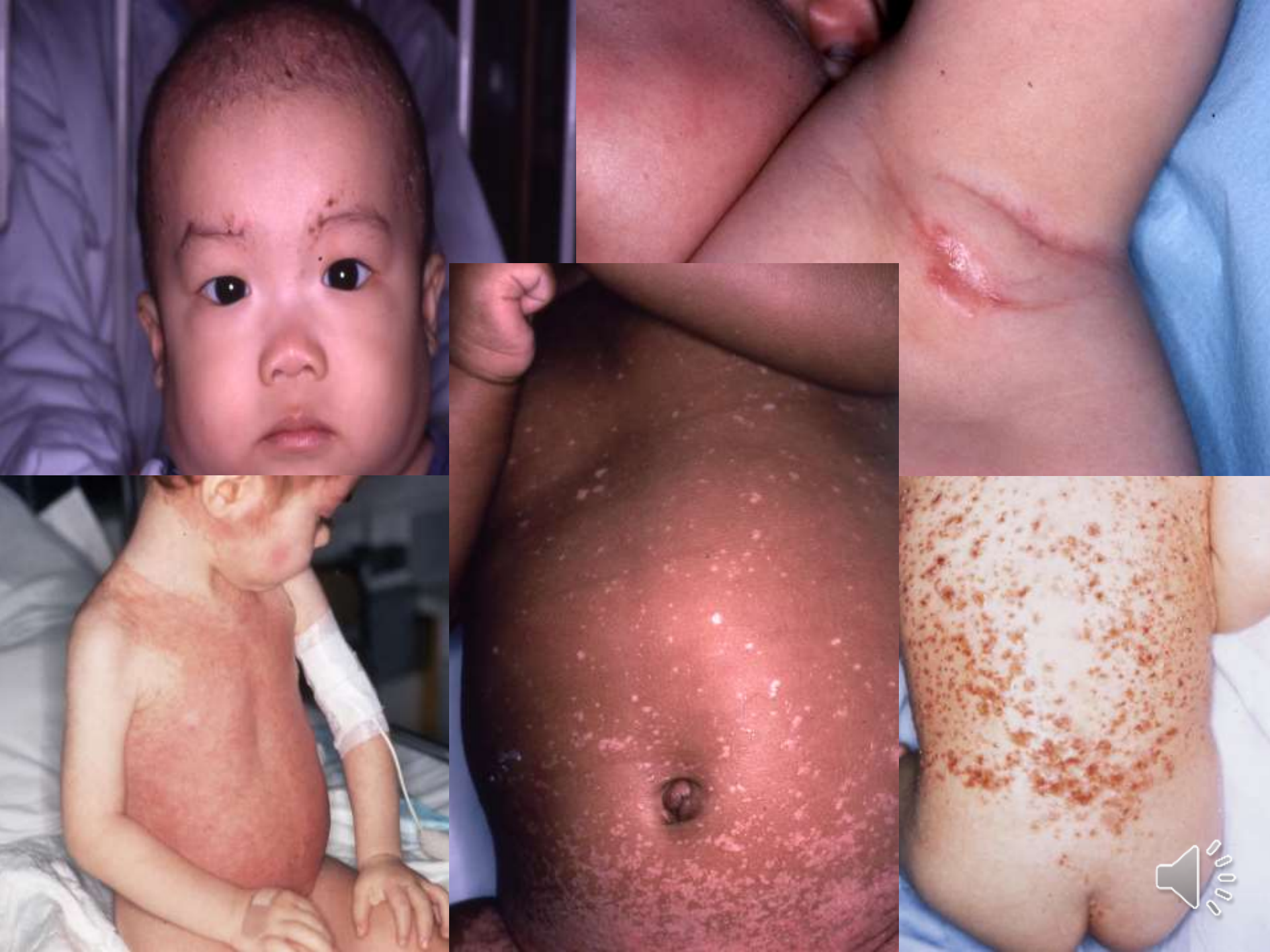




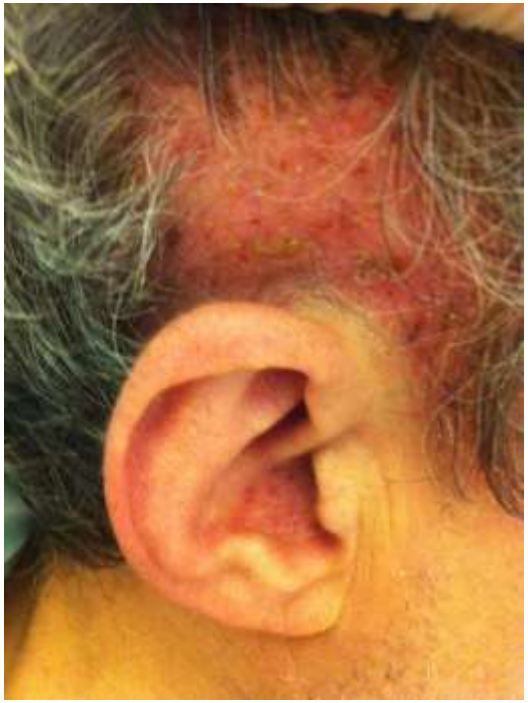
Lésions papulo-crouteuses, purpuriques, localisée versus diffuses

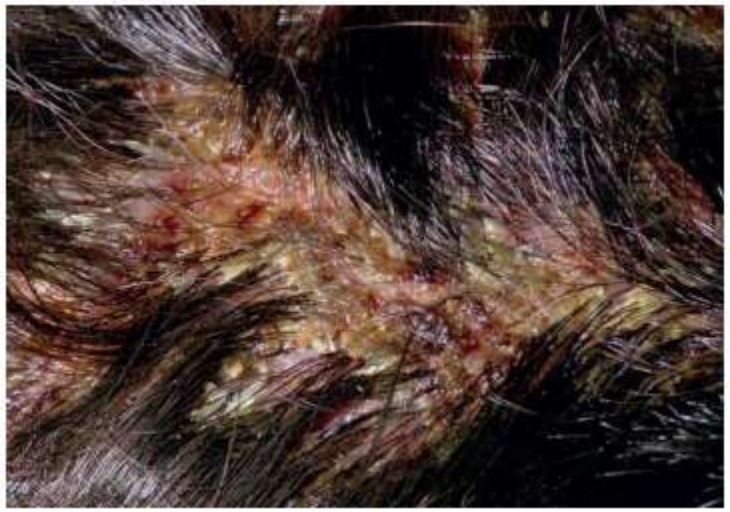
Emile, Blood 2016, Saurat 2017



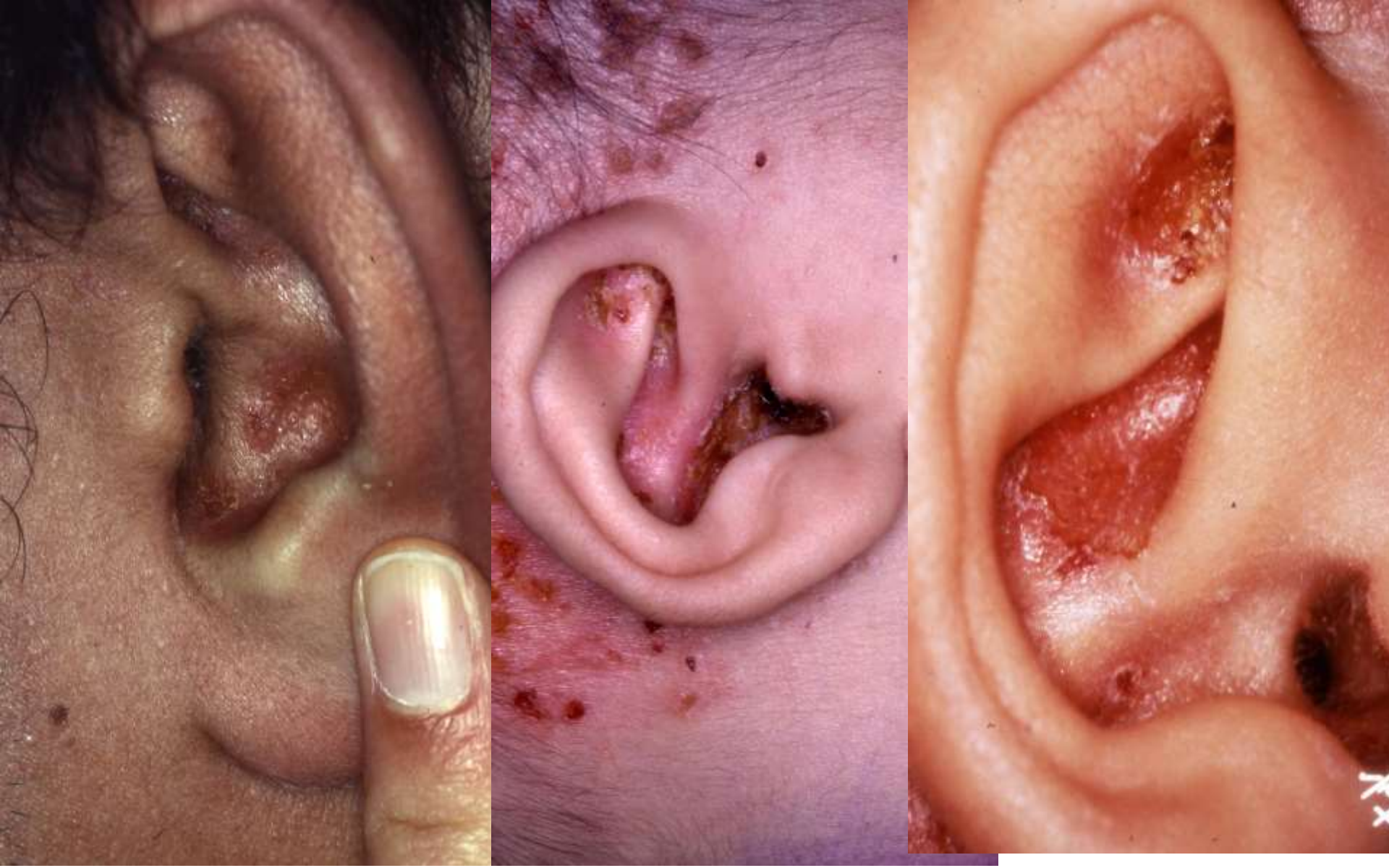
Histiocytose Langerhansienne

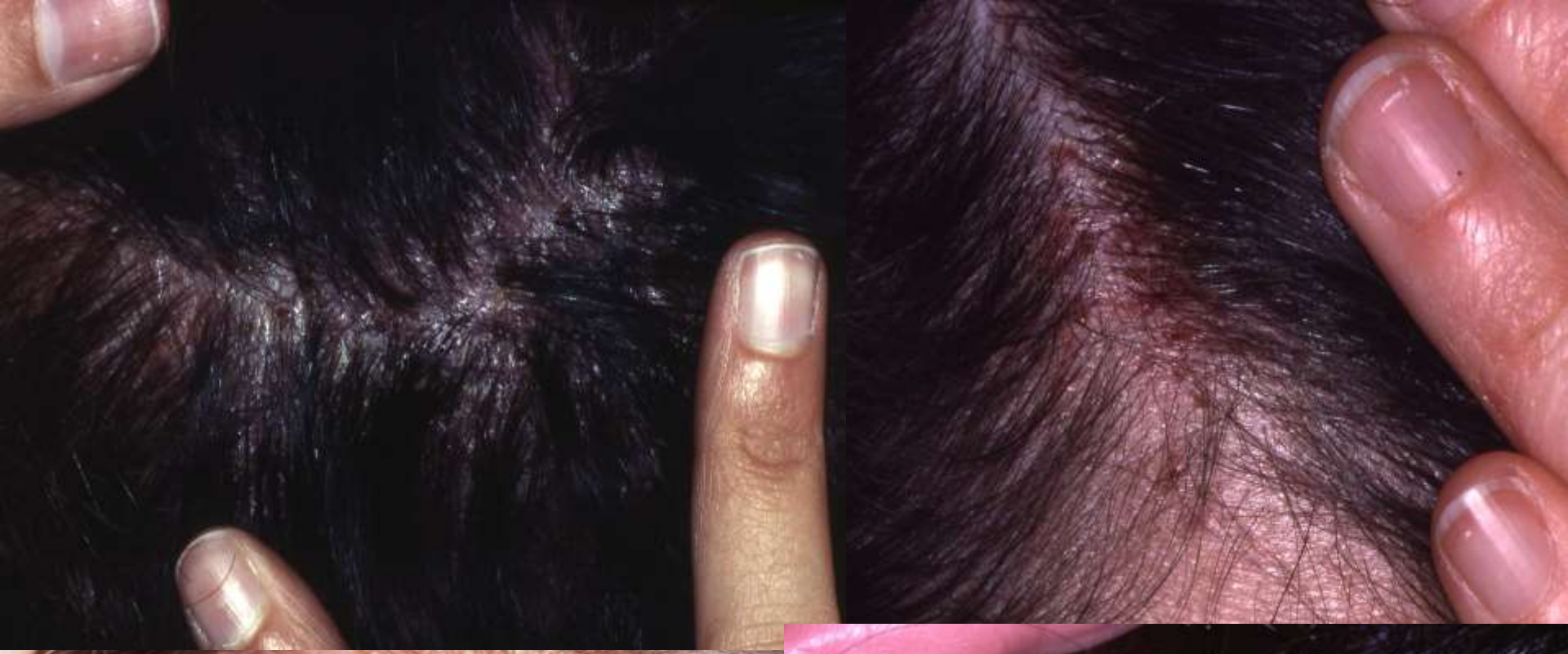


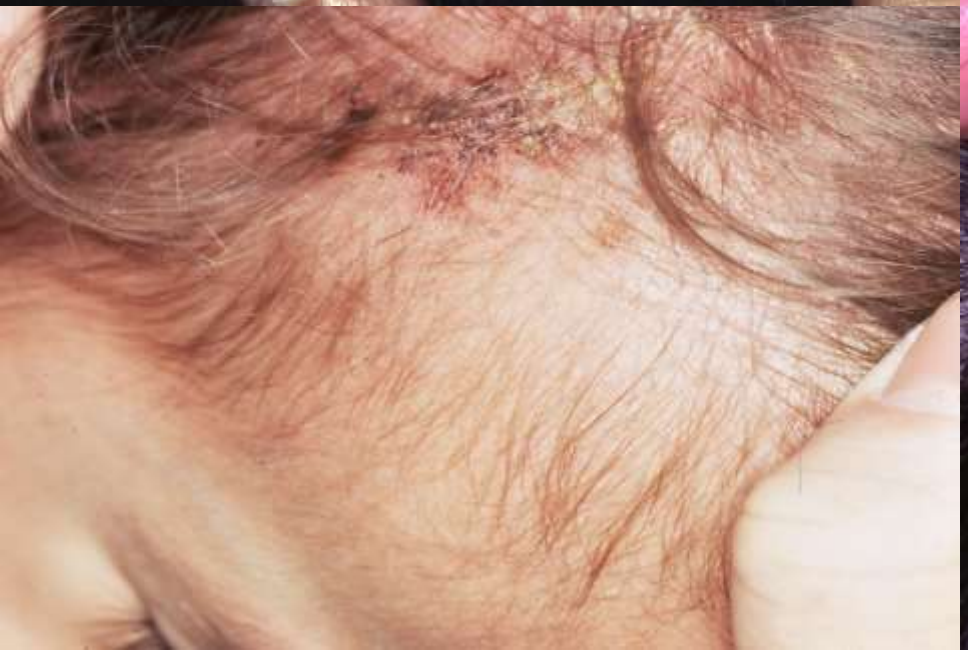


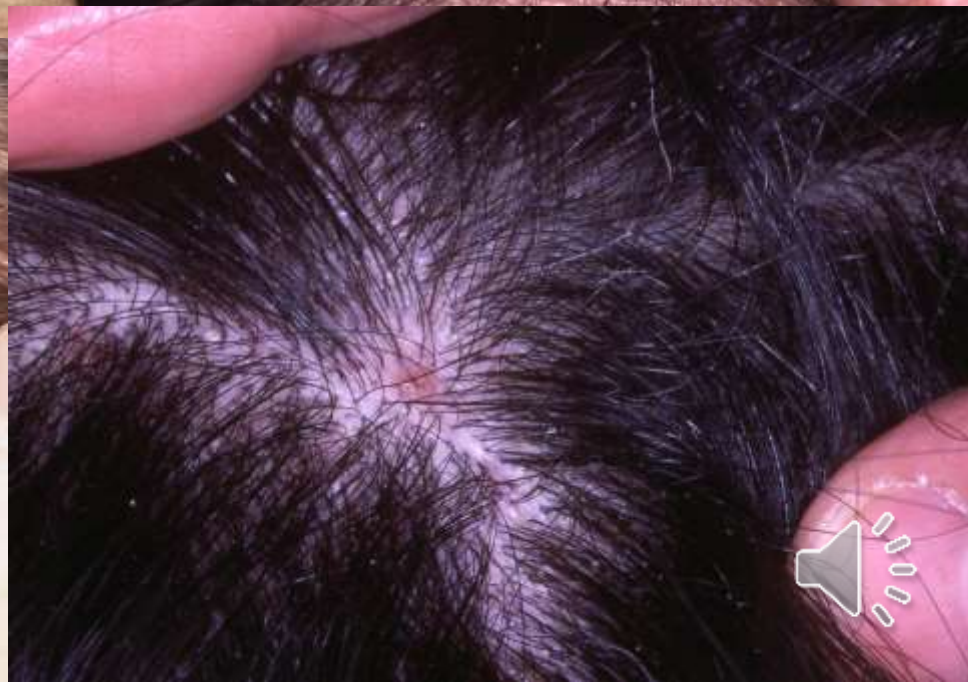
Lésions érythémateuses, crouteuses ou pustuleuses du cuir chevelu

Photo personnelle, Saurat 2017

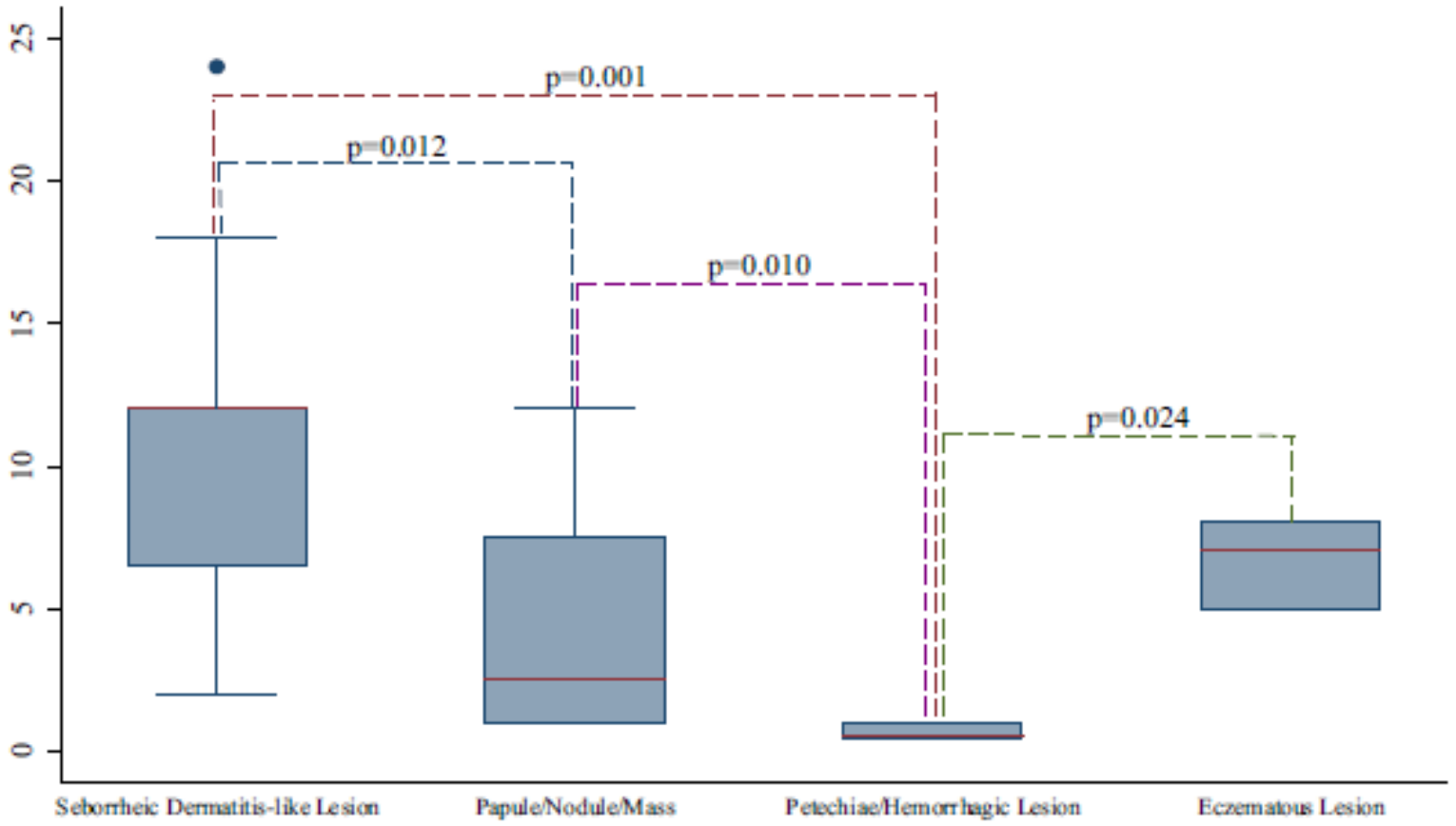








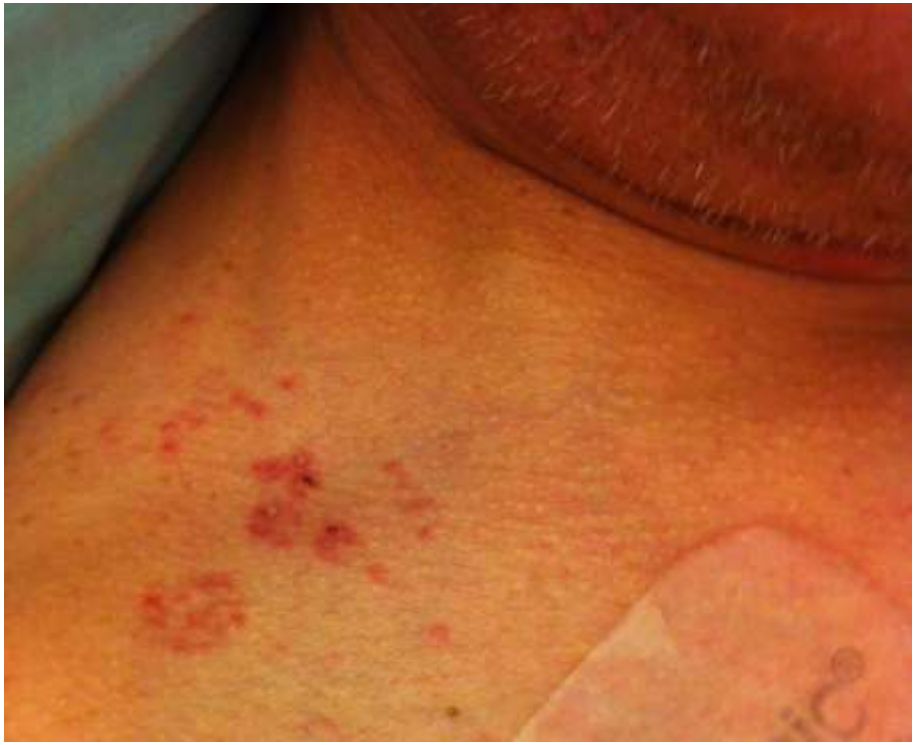
Histiocytose Langerhansienne

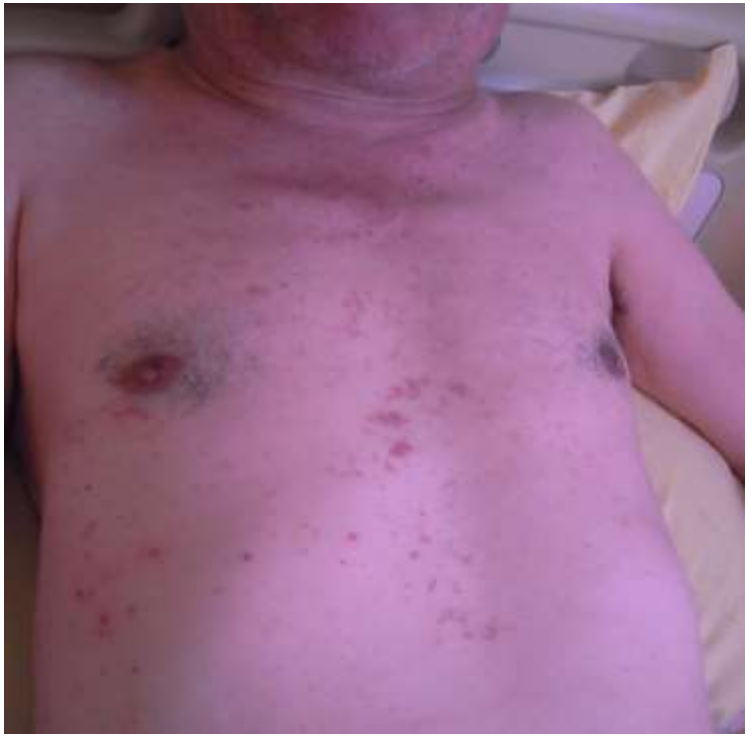


Plus de retard diagnostique dans les formes avec atteinte DS-like

Poompuen, Eur Journal of Pediatrics 2019

Histiocytose Langerhansienne

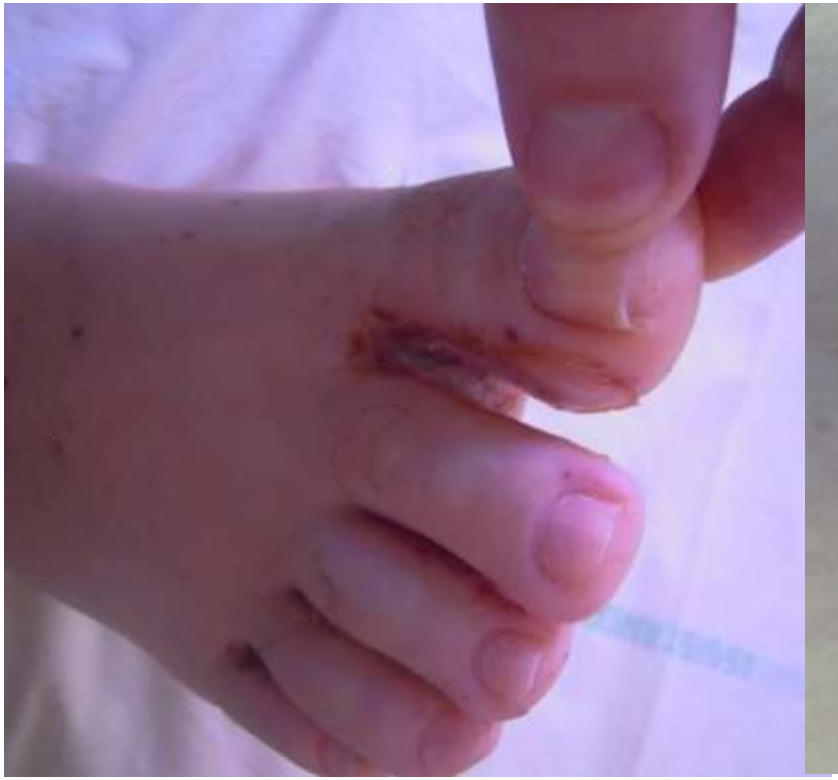


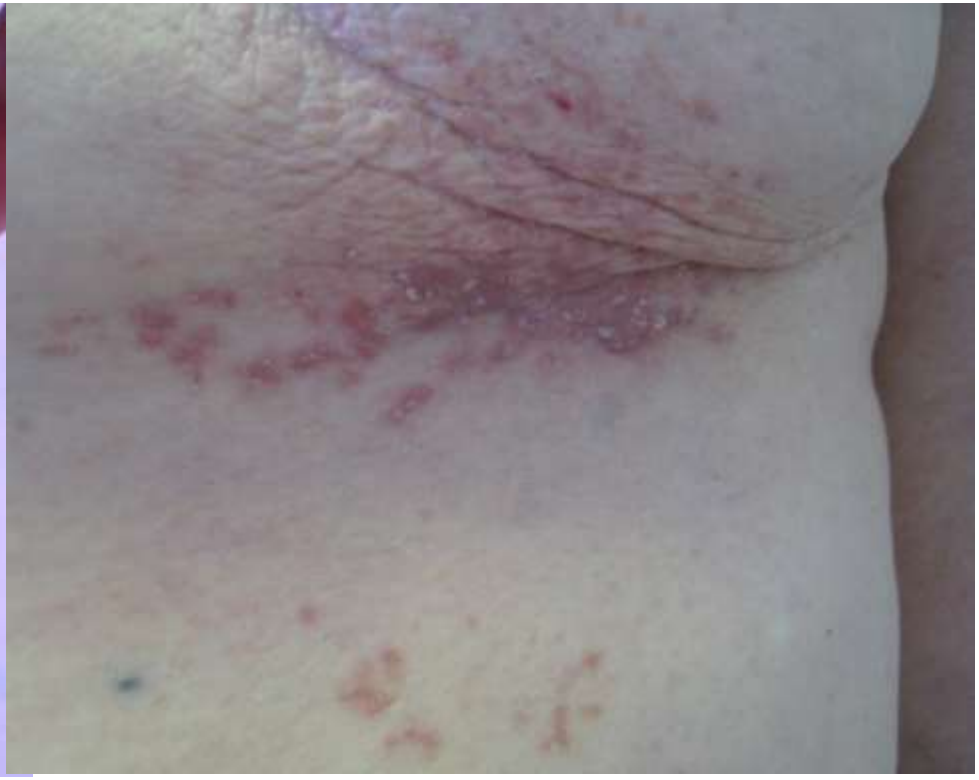


Lésions papulo-crouteuses +/- pustuleuses
localisées versus diffuses

Photos personnelles

Histiocytose Langerhansienne





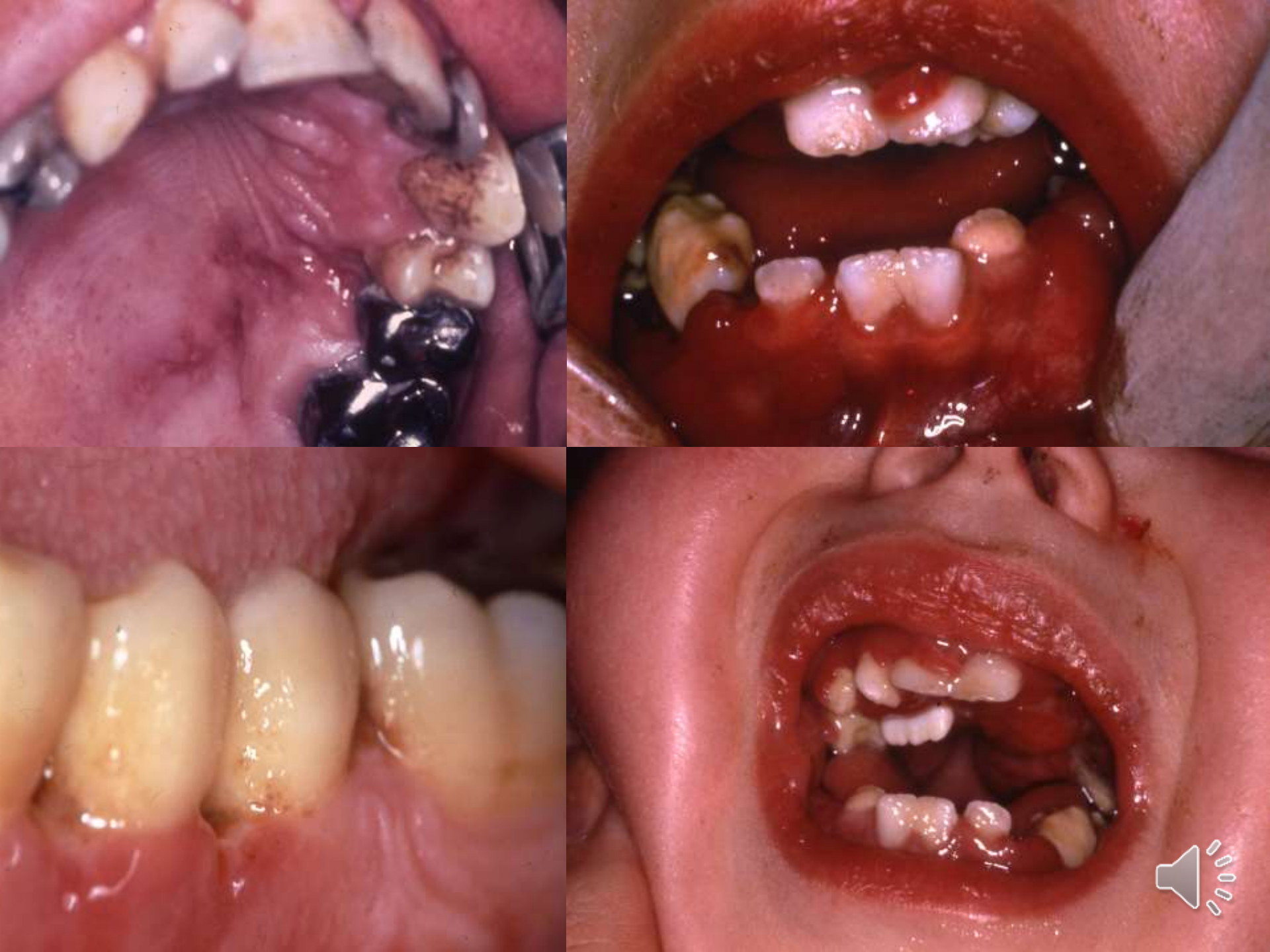
Intertrigo aseptique crouteux, +/- suintant

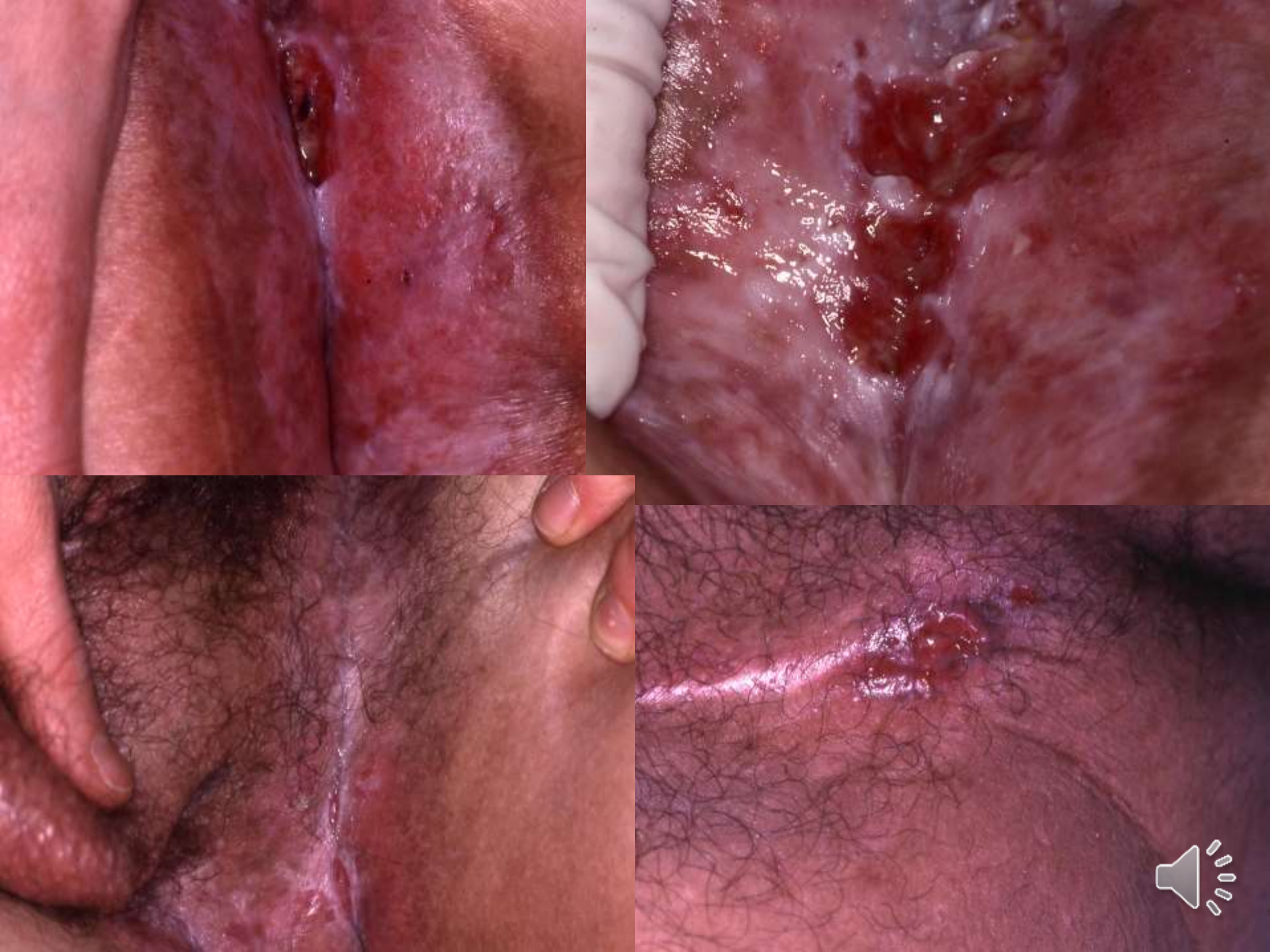
Photos personnelles

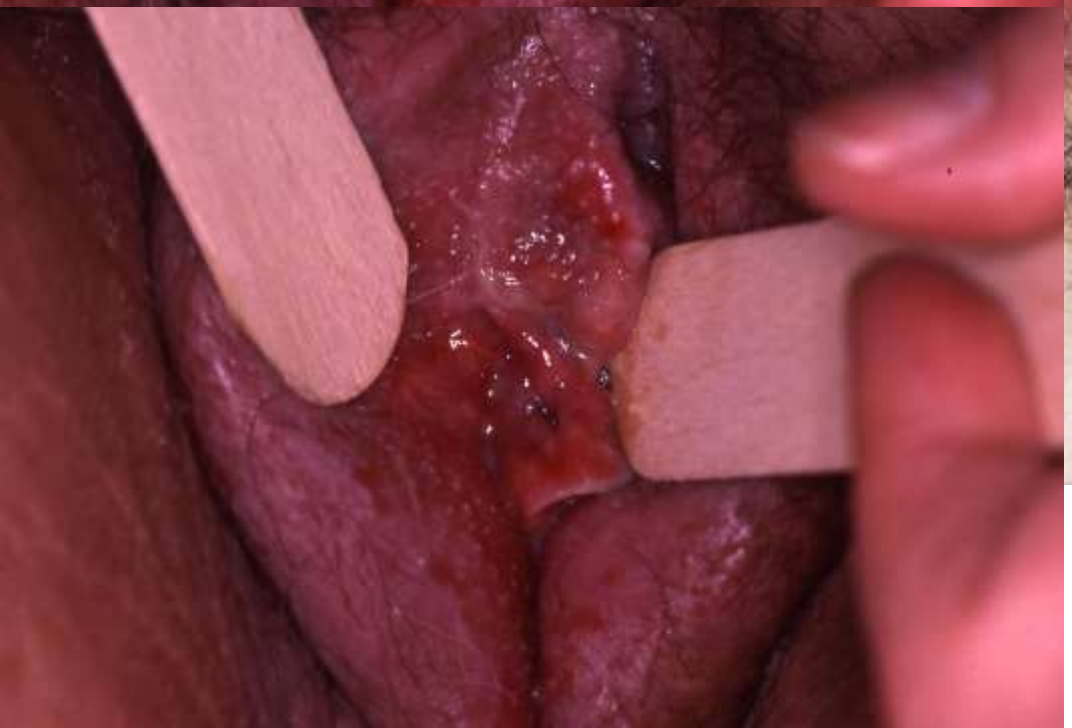
Histiocytose Langerhansienne

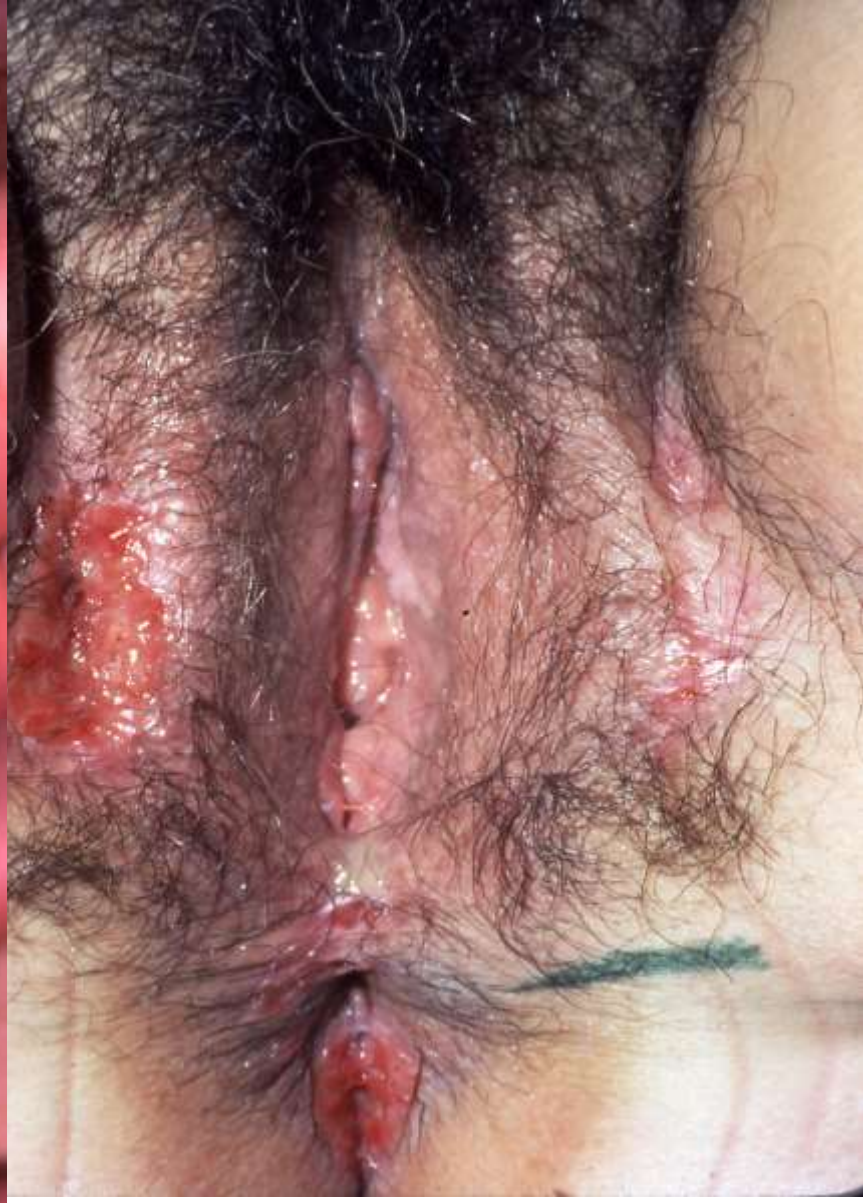
Erosions vulvaires crouteuses

Photos personnelles





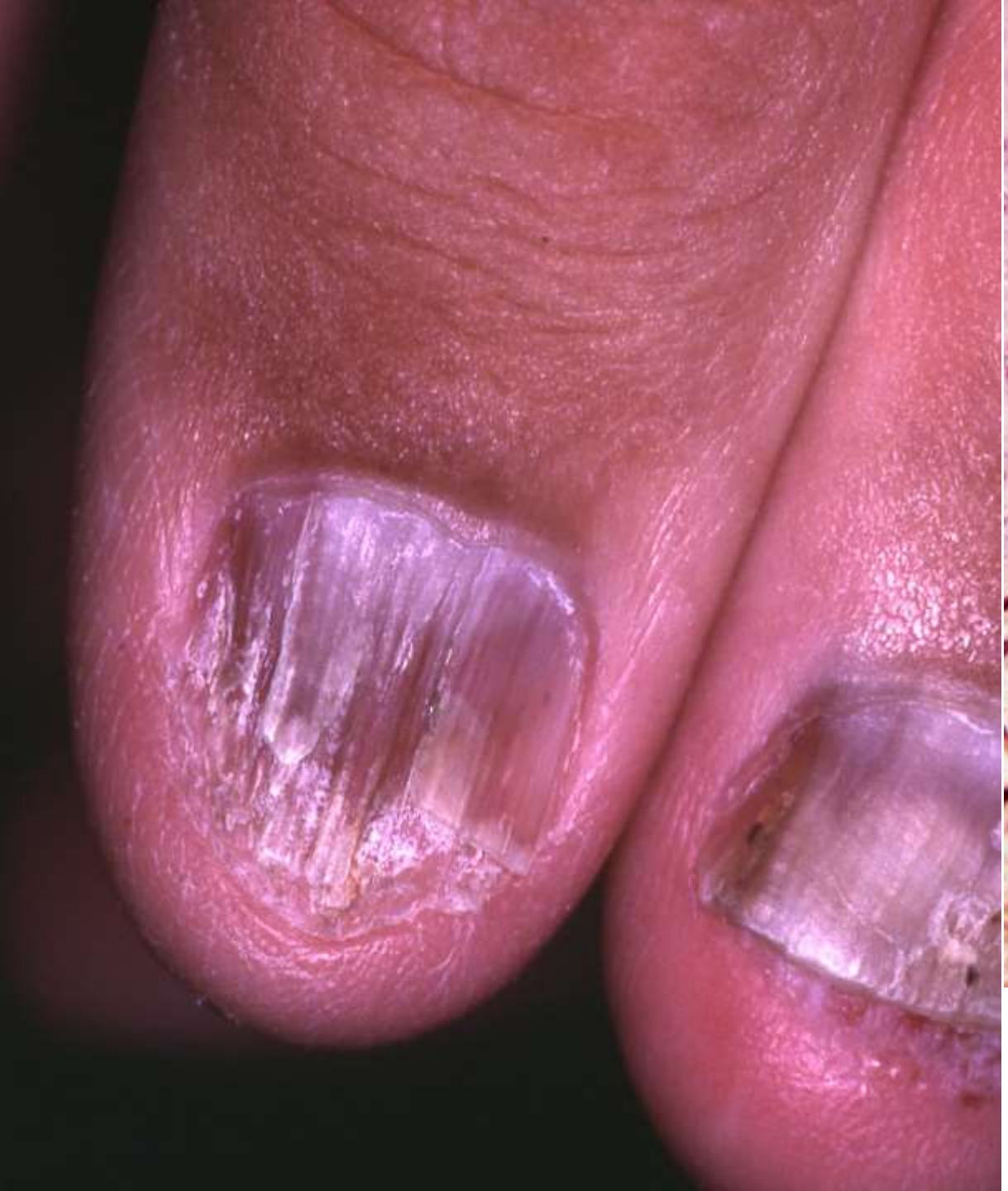


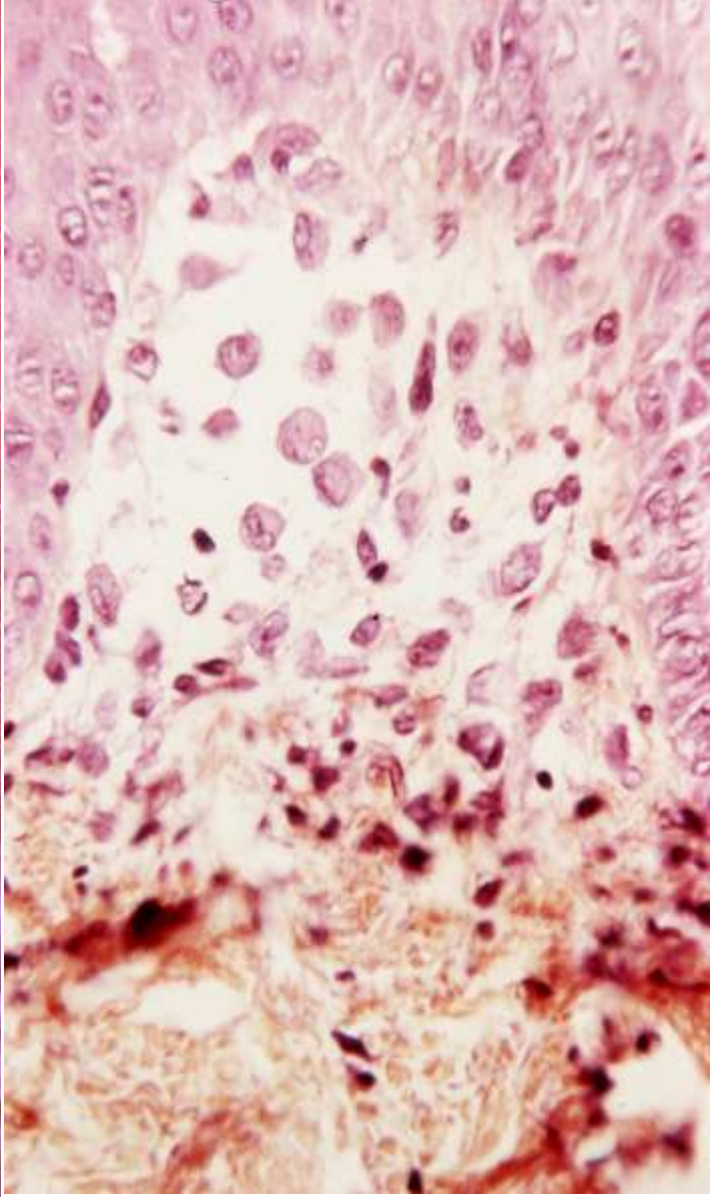


Histiocytose Langerhansienne

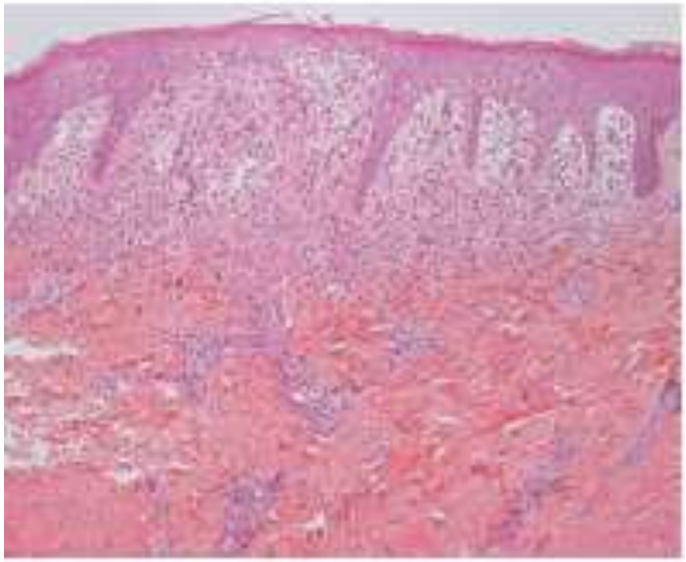
- Atteinte lichénoïde unguéale
- Associée à un mauvais pronostic ?

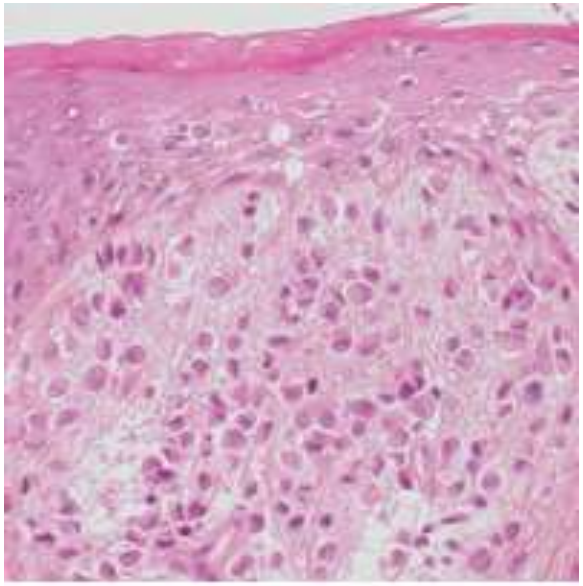
Crickx Acta derm 2017, Saurat 2017

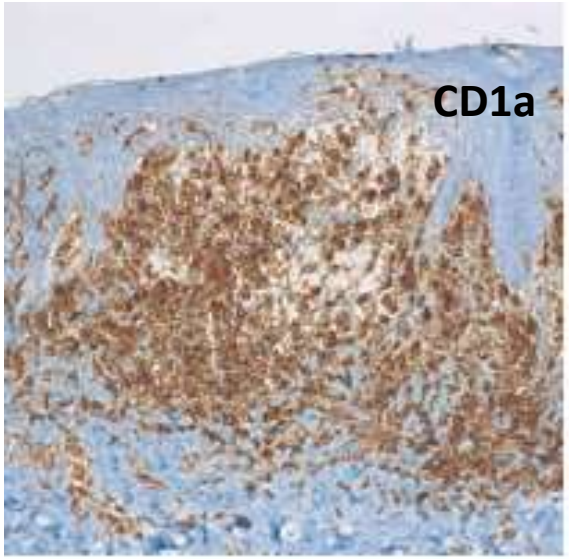




Histiocytose Langerhansienne



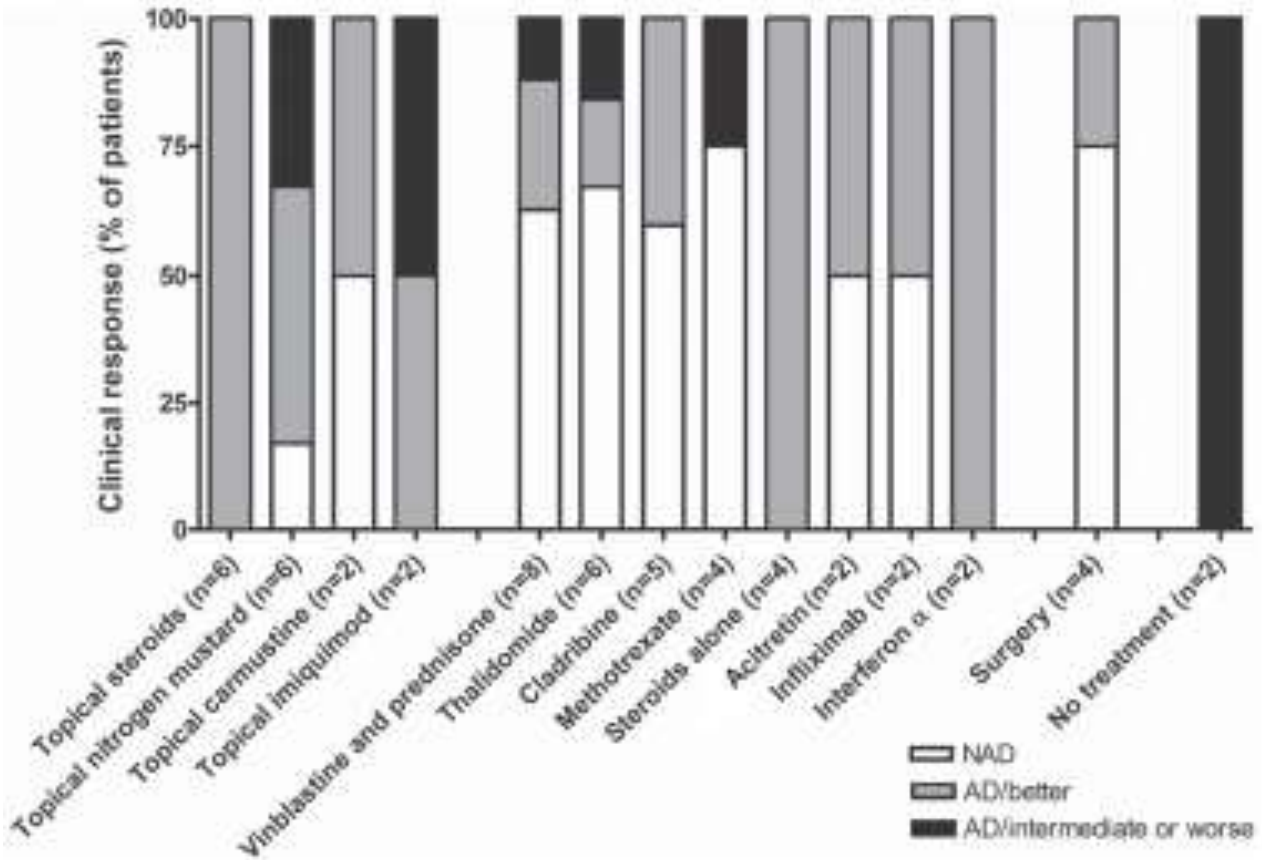




Infiltrat sous épidermique, épidermotropisme fréquent
Cellules de grandes tailles, cytoplasme éosinophile, noyau réniforme
Infiltrat lymphocytaire et éosinophile associé
Marquage CD1a + CD207+ (Langerhine), CD68+, PS100+/-
Attention CD207+ obligatoire si uniquement CD1a+ ICH: indeterminate cell histiocytosis

Parfois association avec histiocytes multinucléés ou xanthomisés (cytoplasme spumeux)
Ulcérations, pustules, purpura fréquent

Traitement de l'atteinte cutanée



- DC
- Carmustine
- CT
- MTX
- Thalidomide
- Acitretine
- Chirurgie

Dépend des autres organes

Crickx Acta derm 2017

Traitement des formes systémiques

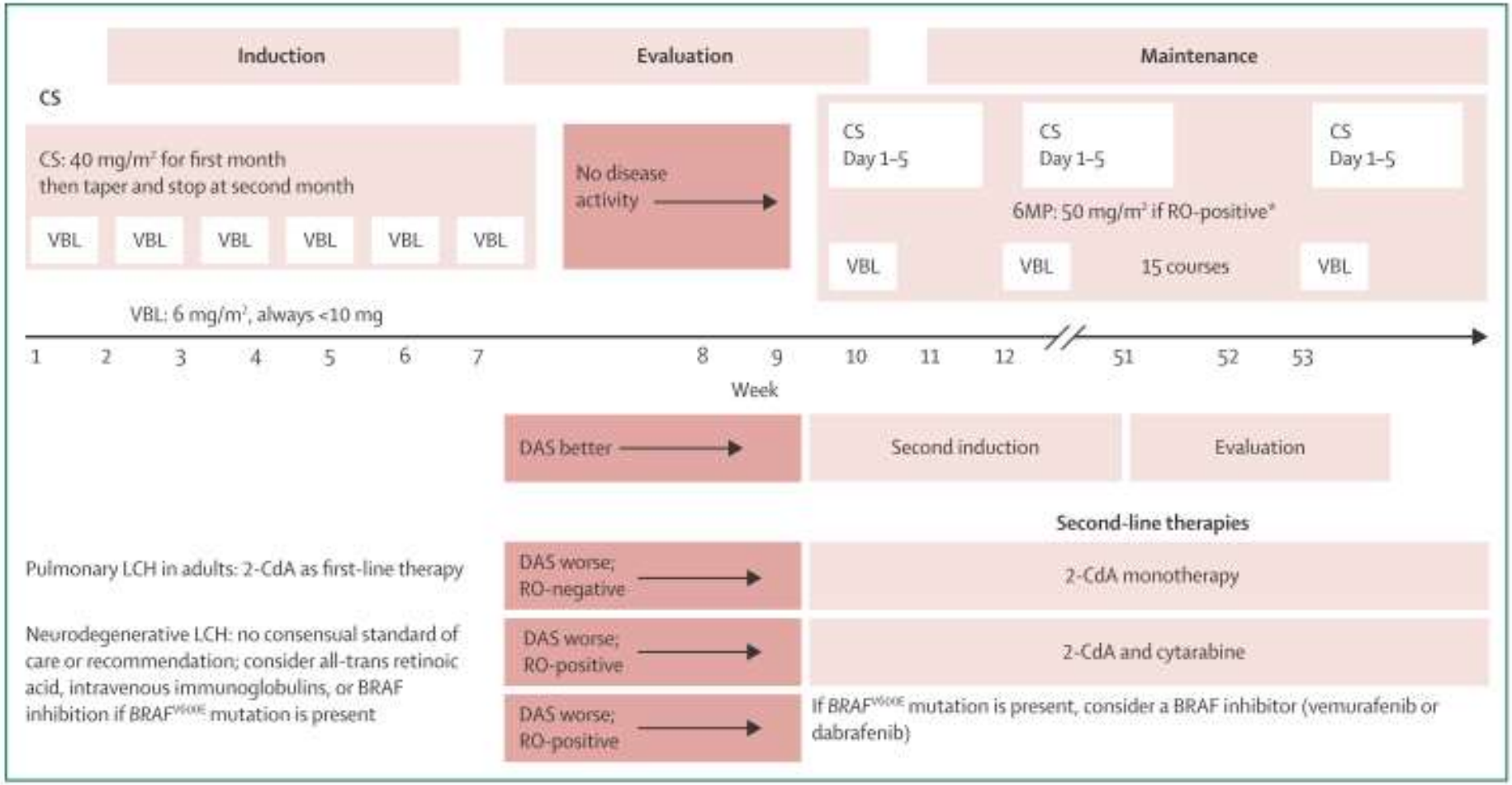


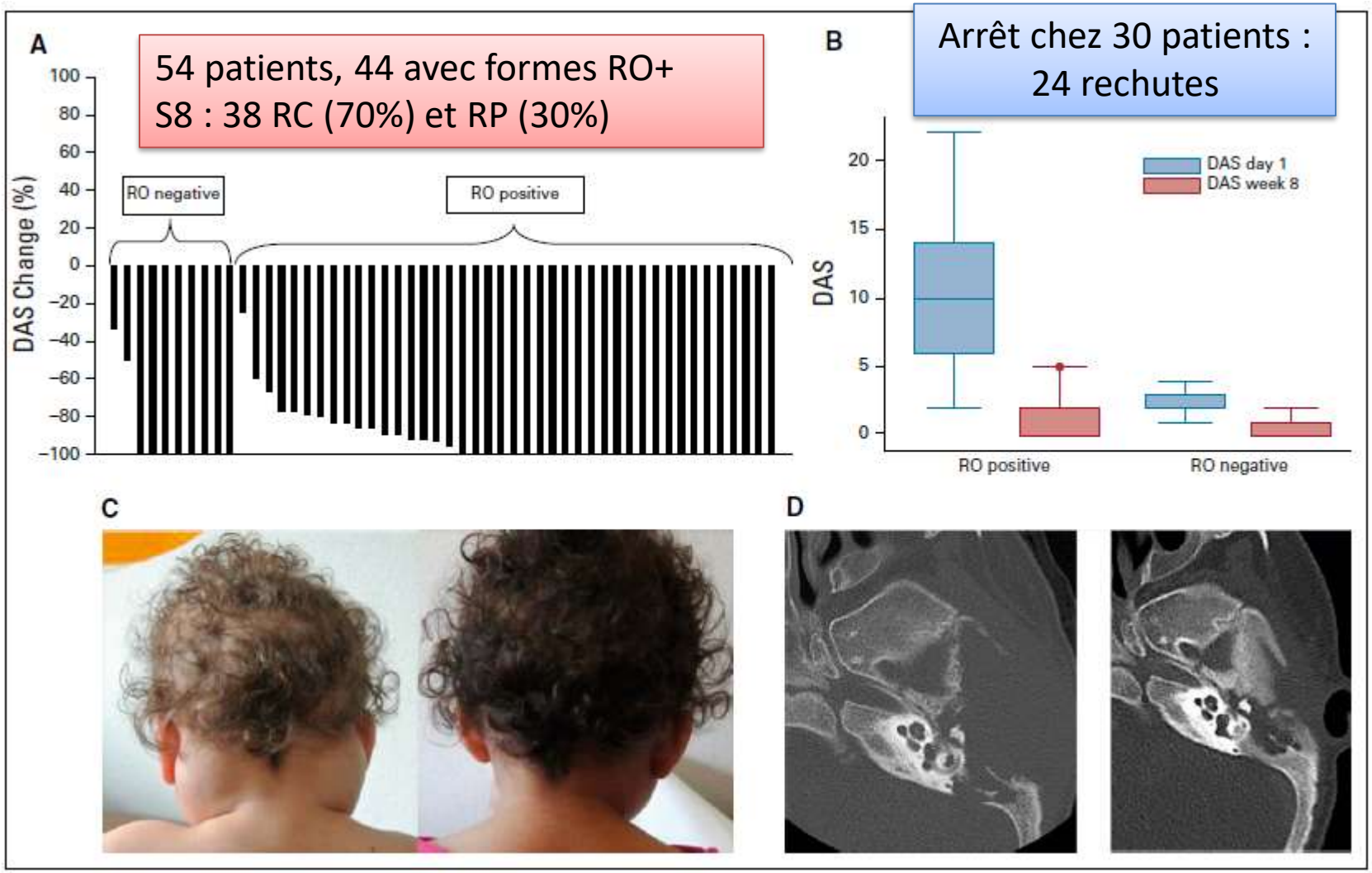
***Figure 4*: Validated therapeutic options for patients with Langerhans cell histiocytosis**
Therapeutic options are recommended in both paediatric and adult populations, despite insufficient studies in adult population. CS=corticosteroid. 6MP=mercaptopurine. VBL=vinblastine. 2-CdA=cladribine or 2-chlorodeoxyadenosine. DAS=disease activity score. RO-positive=risk organ involved. RO-negative=no risk organ involved. LCH=Langerhans cell histiocytosis. *Haematological system, which is almost always associated with spleen and liver involvement.

Haroche Lancet Oncol 2017

Inhibiteurs de BRAF et histiocytose Langerhansienne

54 patients, 44 avec formes RO+
S8 : 38 RC (70%) et RP (30%)

Arrêt chez 30 patients :
24 rechutes



E.I : rash cutanée : 74%

Donadieu, JCO 2019

Histiocytose Langerhansienne et autres hémopathies

CLINICAL AND LABORATORY INVESTIGATIONS

BJD
British Journal of Dermatology

Langerhans cell histiocytosis first presenting in the skin in adults: frequent association with a second haematological malignancy

J.R. Edelbroek,[1] M.H. Vermeer,[1] P.M. Jansen,[2] T.J. Stoof,[3] M.M.D. van der Linden,[4] B. Horváth,[5] J. van Baarlen[6] and R. Willemze[1]

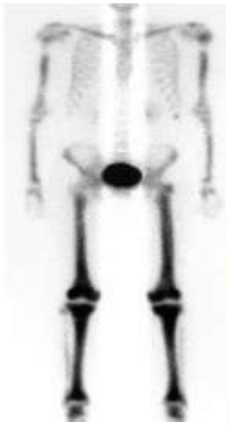
Departments of [1]Dermatology and [2]Pathology, Leiden University Medical Center, Leiden, the Netherlands
[3]Department of Dermatology, Vrije Universiteit Medical Center, Amsterdam, the Netherlands
[4]Department of Dermatology, Academic Medical Center, Amsterdam, the Netherlands
[5]Department of Dermatology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands
[6]Laboratorium Pathologie Oost-Nederland, Enschede, the Netherlands

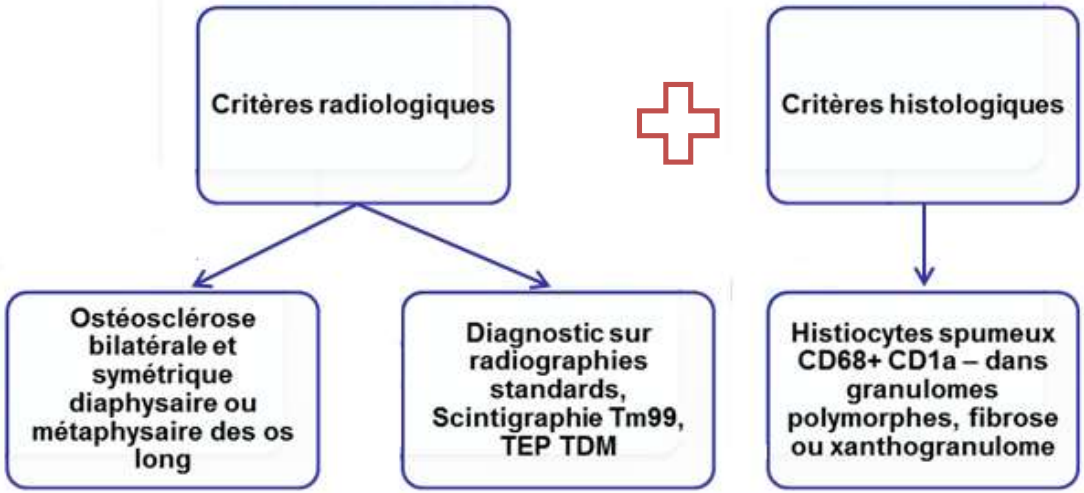
- 16 patients adultes LCH débutant par atteinte cutanée
- 5 hémopathies: 2 LMMC, 1 lymphome B grande cellule, 1 lymphome T périphérique, sarcome histiocytaire

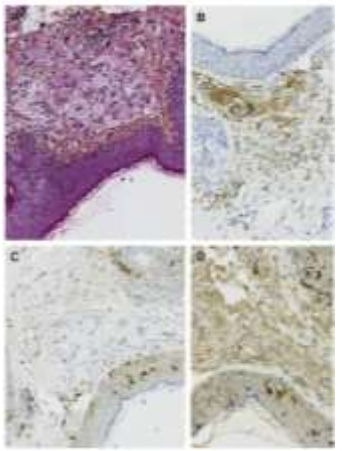
Maladie d'Erdheim-Chester

- Appartient également au groupe L de la nouvelle classification des histiocytoses
- Formes mixtes décrites: MEC + histiocytose langerhansienne (HL)
  ou MEC + Rosai-Dorfman Hervier B *Blood* 2014.
- Mutation BRAF V600E: 54% d'une série de 37 patients
- Activation de la voie des MAPK 100% des cas Diamond Cancer Discovery 2016
- Efficacité du Vemurafenib Haroche J et al *JCO 2014*
- Critères diagnostiques proposés en 2015, inclusion BRAF V600E critères 2020

et sequencing pathway MAPK-ERK







Si négatifs atteinte organes typiques

BRAF

Diamond et al. Blood 2015
Goyal Blood 2020

Maladie d'Erdheim-Chester

Table 1. Histiocytoses of the L group

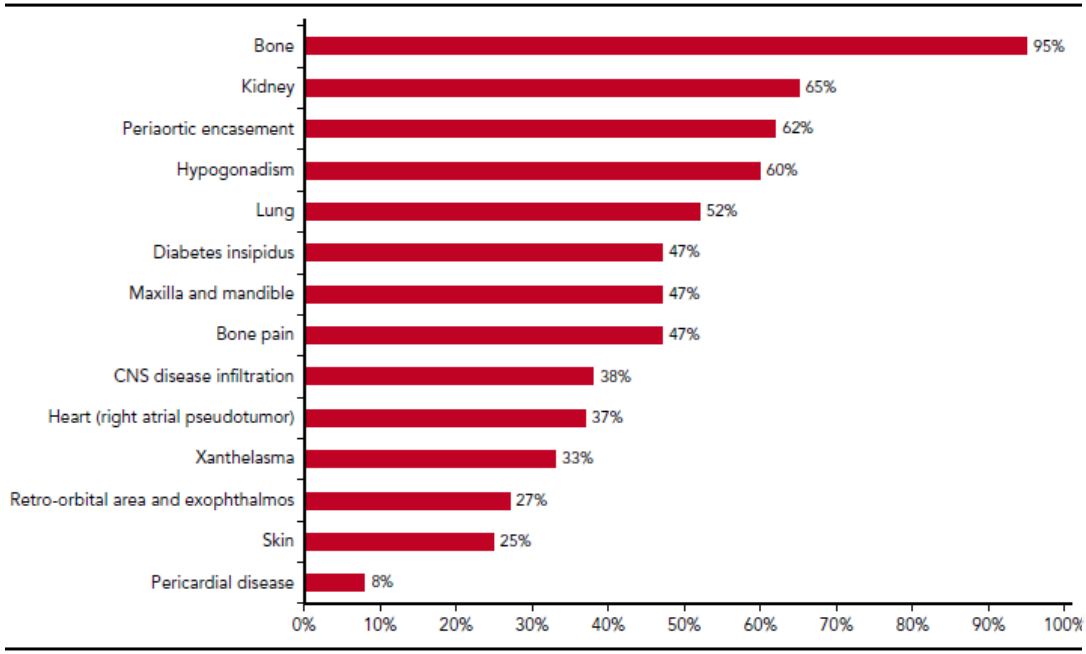
Disease	Subtypes
LCH	LCH SS
	LCH lung^{+}
	LCH MS-RO^{+}
	LCH MS-RO^{-}
	Associated with another myeloproliferative/ myelodysplastic disorder
ICH	
ECD	ECD classical type
	ECD without bone involvement
	Associated with another myeloproliferative/ myelodysplastic disorder
	Extracutaneous or disseminated JXG with MAPK-activating mutation or ALK translocations
Mixed ECD and LCH	

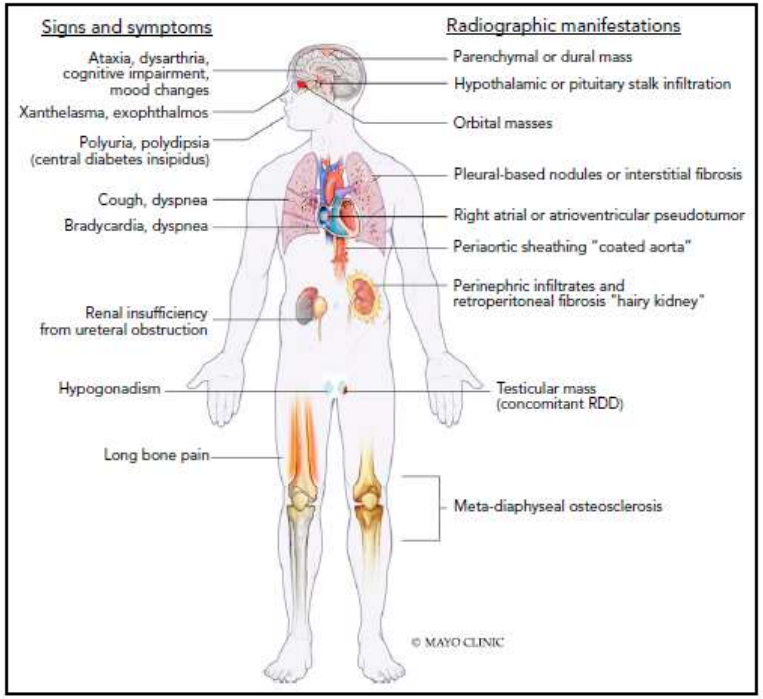
ECD, Erdheim-Chester disease; ICH, indeterminate cell histiocytosis; LCH, Langerhans cell histiocytosis; MS, multiple system; RO, risk organ; SS, single system.

Emile, Blood 2016

Maladie d'Erdheim-Chester

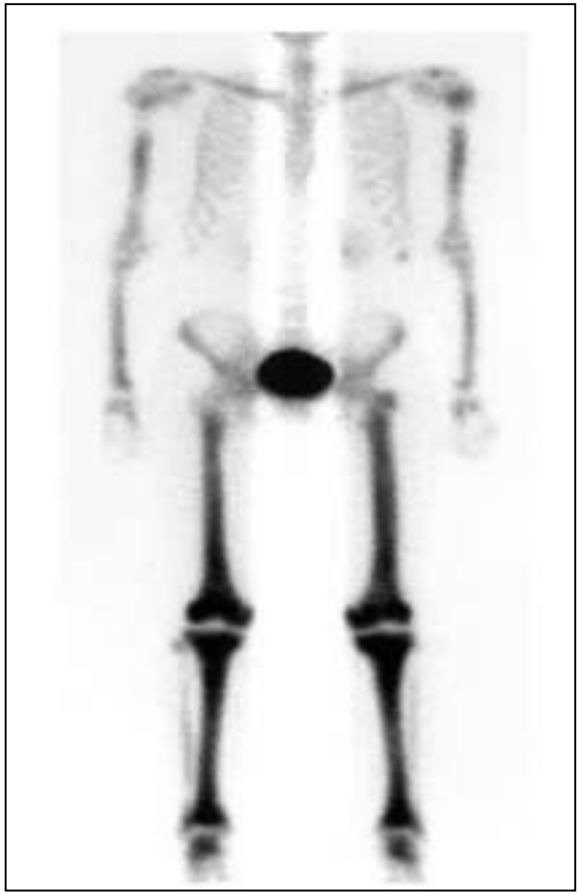
Résumé des atteintes cliniques





Goyal Blood 2020

Maladie d'Erdheim-Chester



- Atteinte osseuse > 95%
- Douleurs osseuses 50%
- Ostéosclérose métaphyso-diaphysaire os long
- Pas d'atteinte axiale ou mandibulaire (HL)
- TEP TDM < genoux ++
- +/- IRM osseux, scinti

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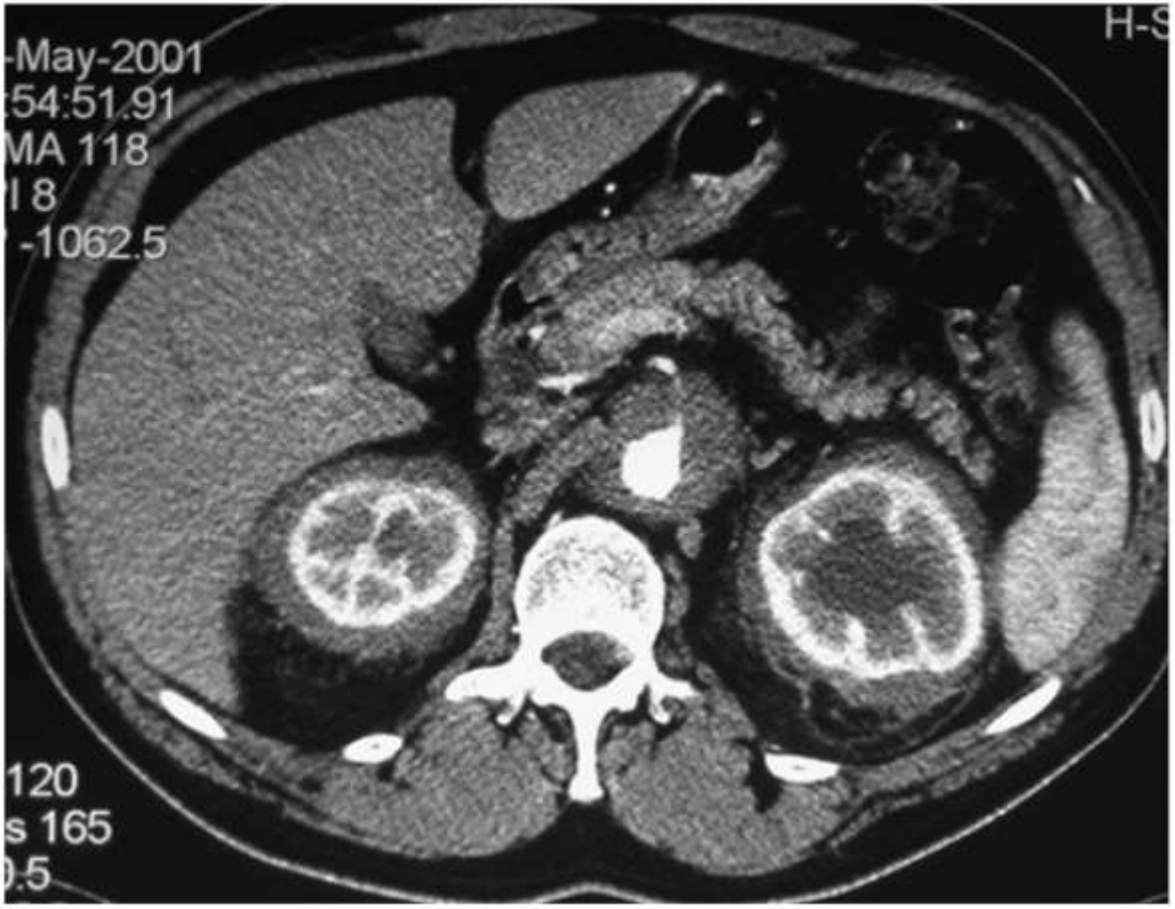


Haroche J *J. Rheum Dis Clin North Am*. 2013

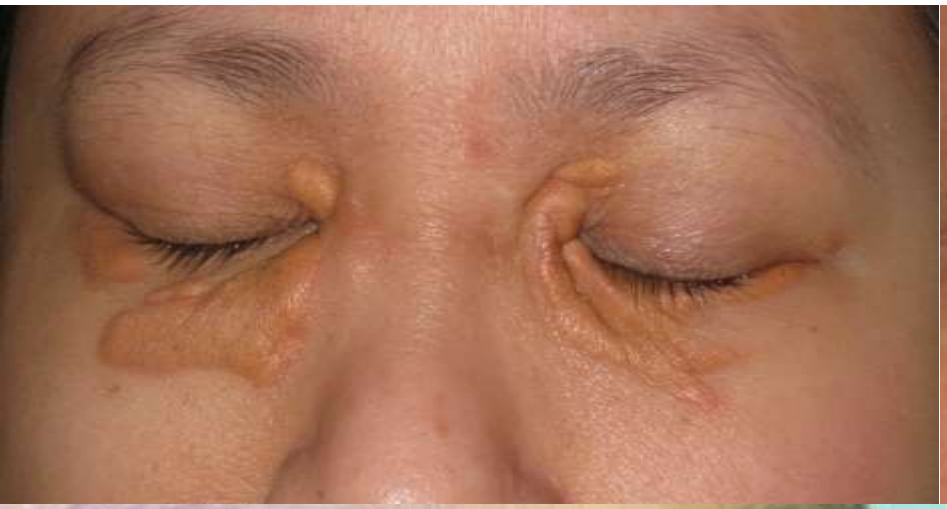
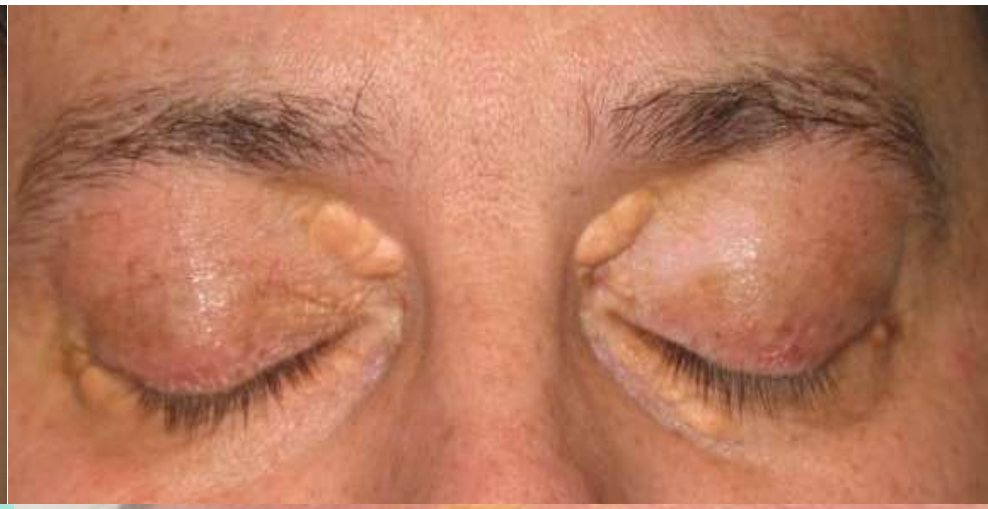
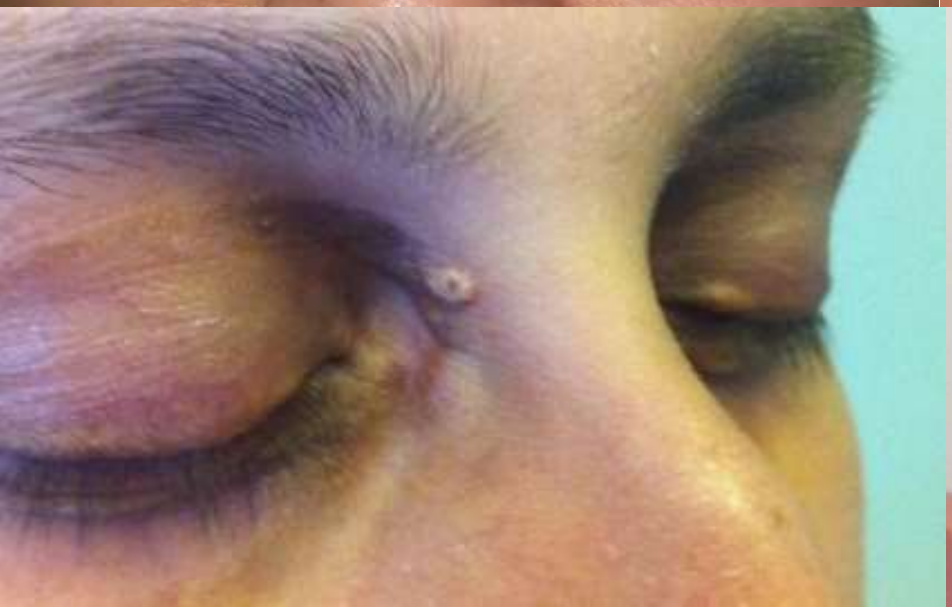
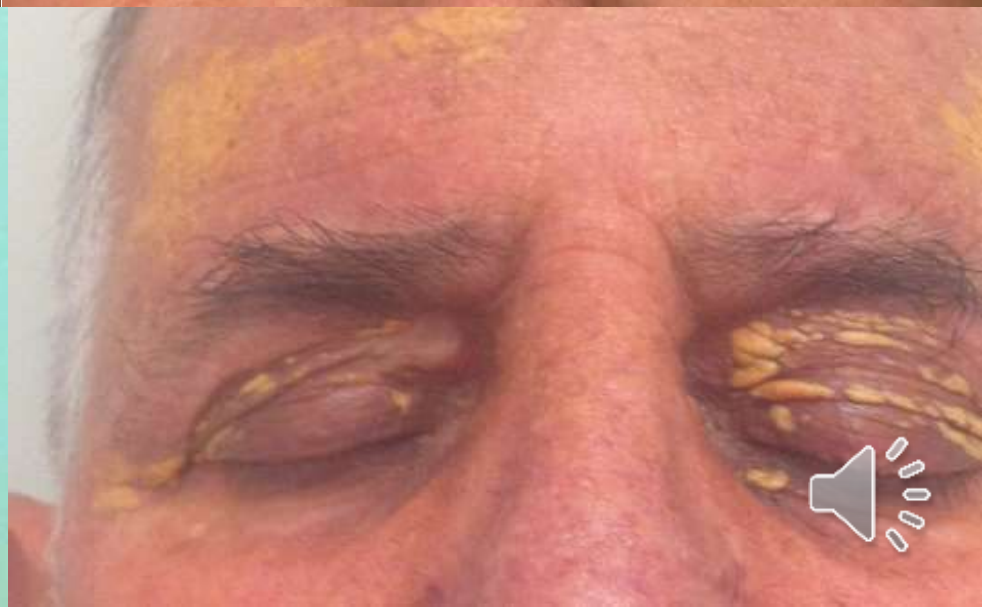
Maladie d'Erdheim-Chester

Caractéristiques des patients	n (%)
MEC avec lésions cutanées	40/123 (32)
MEC isolée MEC+ HL avec lésions cutanées	31 (25) 9 (7)
Sexe masculin	27 (67)
Age médian au diagnostic (extrêmes)	54,5 (26-81)
Atteinte cutanée comme premier symptôme *	12 (30)
Apparition de lésions cutanées avant diagnostic de MEC*	26 (79)
Xanthélasma-like	31 (77)
Autres lésions cutanées spécifiques de MEC (lésions/patients)	11/9 (27/22)
Lésions cutanées d'HL associées	8/6 (20/15)
Diagnostic histologique de MEC sur l'atteinte cutanée	14 (36)
Statut BRAF*	25 (76)

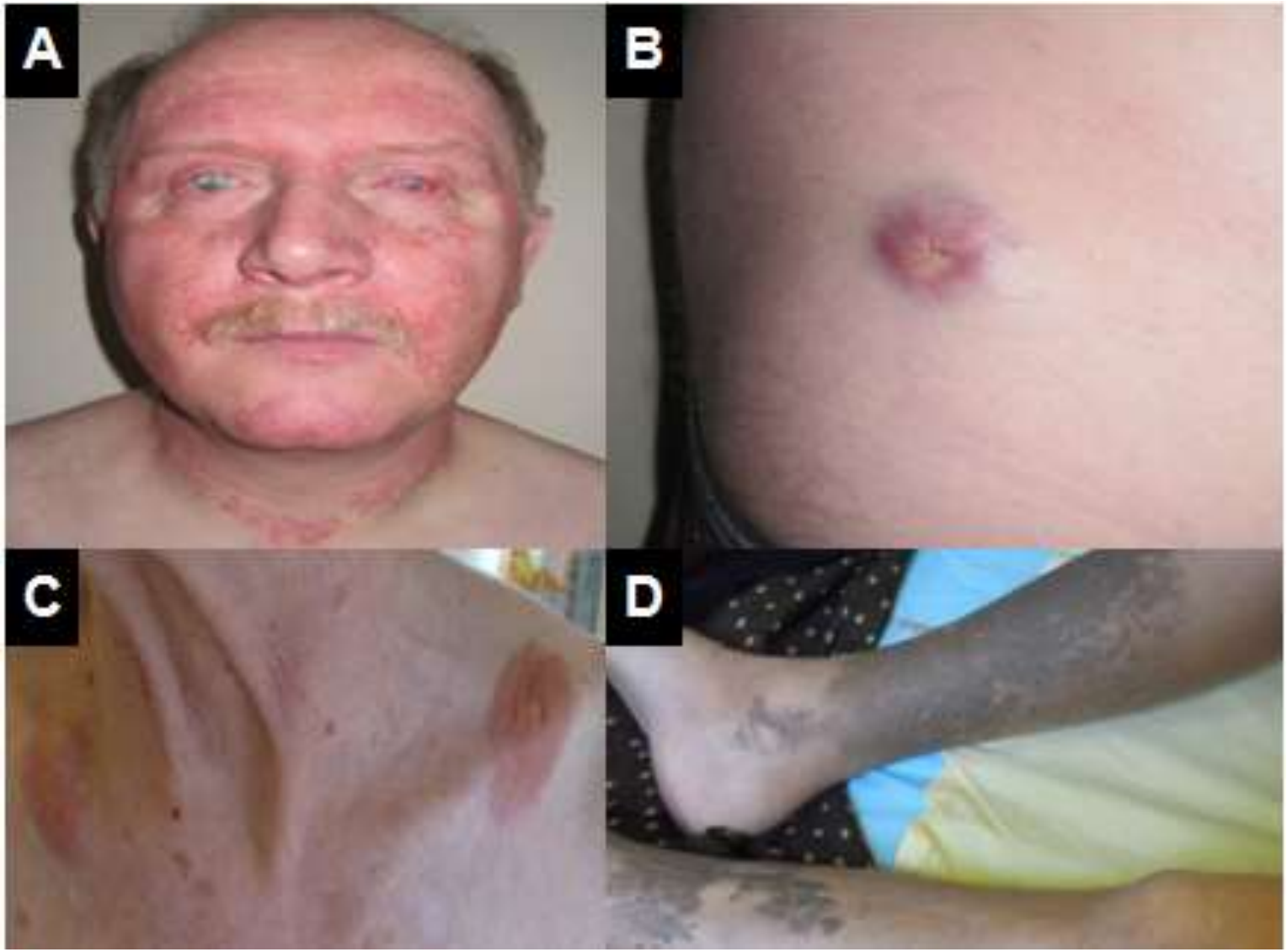
* Parmi les données disponibles

Chasset JAAD 2016

Maladie d'Erdheim-Chester

Maladie d'Erdheim-Chester



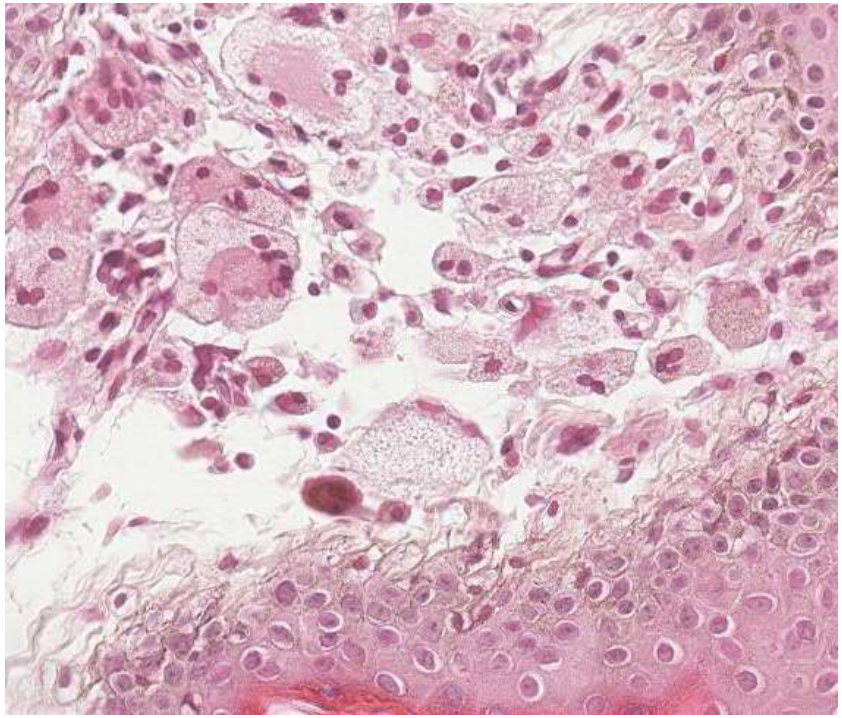
Chasset, JAAD 2016

Maladie d'Erdheim-Chester

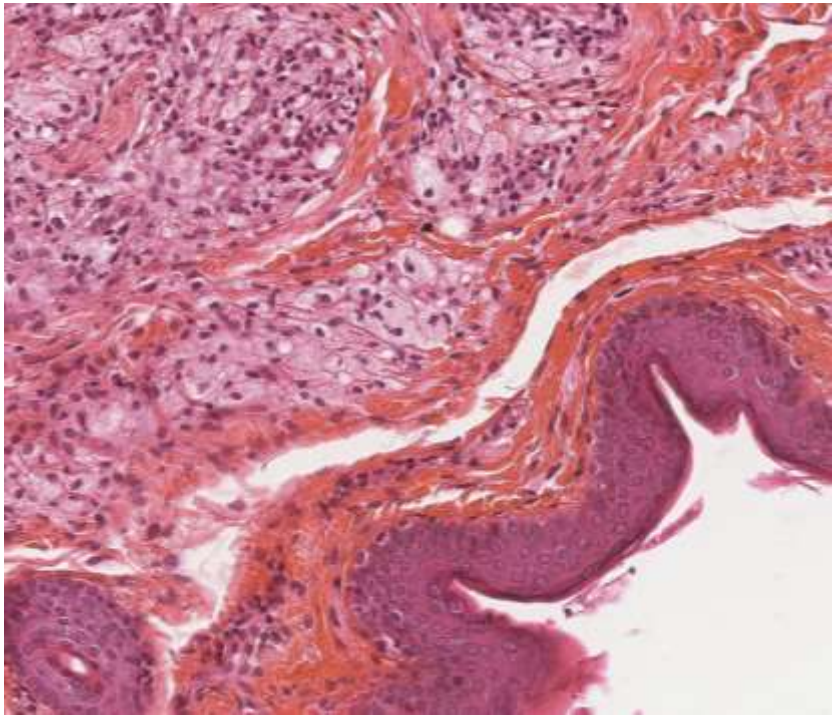
Caractéristiques histologiques xanthélasma (XMA) MEC versus « classique »			
Caractéristiques	**XMA MEC**	**XMA « classique »**	**p**
Topographie infiltrat derme profond	5/7	9/14	1
Topographie infiltrat hypoderme	3/7	0/14	0,02
Nombreuses cellules multinuclées	3/7	0/14	0,02
Nombreuses cellules Touton	5/7	1/14	0,005*
Nombreuses cellules spumeuses	7/7	14/14	1
Fibrose	3/7	14/14	0,005*
CD68 > 50% cellules spumeuses	7/7	14/14	1
CD163 > 50% cellules spumeuses	7/7	14/14	1
CD1a	0/7	0/14	1
JAG2	0/7	0/14	1
FXIII > 30% cellules spumeuses	7/7	3/14	0,001*

* Demeure statistiquement significatif après correction par test de Bonferroni

Maladie d'Erdheim-Chester



Xanthelasma MEC



Xanthelasma « classique »

Chasset, JAAD 2016

Atteinte dermatologique maladie d'Erdheim-Chester

Histiocytic disorder	N = 15
ECD alone	14
Mixed ECD and Langerhans cell histiocytosis	1
Sex	
Men	9
Women	6
Ethnicity	
White	12
Asian	2
African American	1
Median age at diagnosis (years) (range)	52 (34–68)
Median survival since diagnosis (years)	3·0
Number alive at last follow up (years)	11
Median number of organ systems involved (range)	5 (2–7)
Other organs involved	
Bone	12
Cardiovascular system	6
Central nervous system	6
Kidneys	5
Lungs	5
Retroperitoneum	5
Adrenal glands	3
Paranasal sinuses	2
Liver	1
Marrow	1
Spleen	1
BRAF V600E status	
Positive	5
Negative	5
Unknown	5

- N=71 ECD

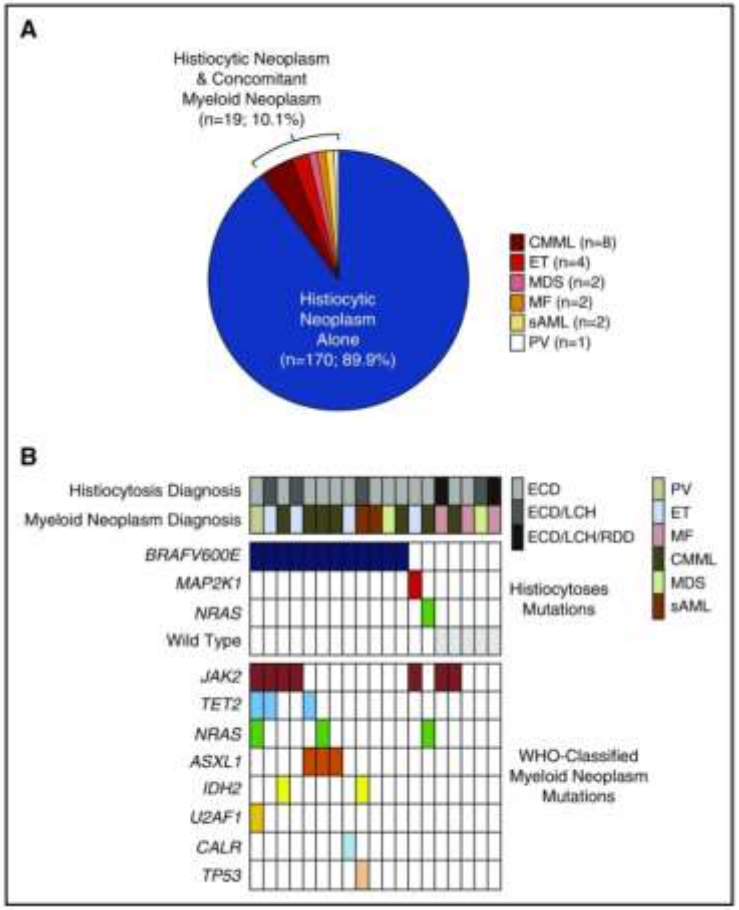
15 (21%) atteinte cutanée

- Xanthelasma like-lesions n=8 (50%)
- Autres :
  - Panniculite
  - Granulome annulaire-like
  - Macules érythémato- squameuses

(histiocytose mixte)

Kobic BJD 2019

ECD, hémopathies myéloïdes et hématopoïèse clonale

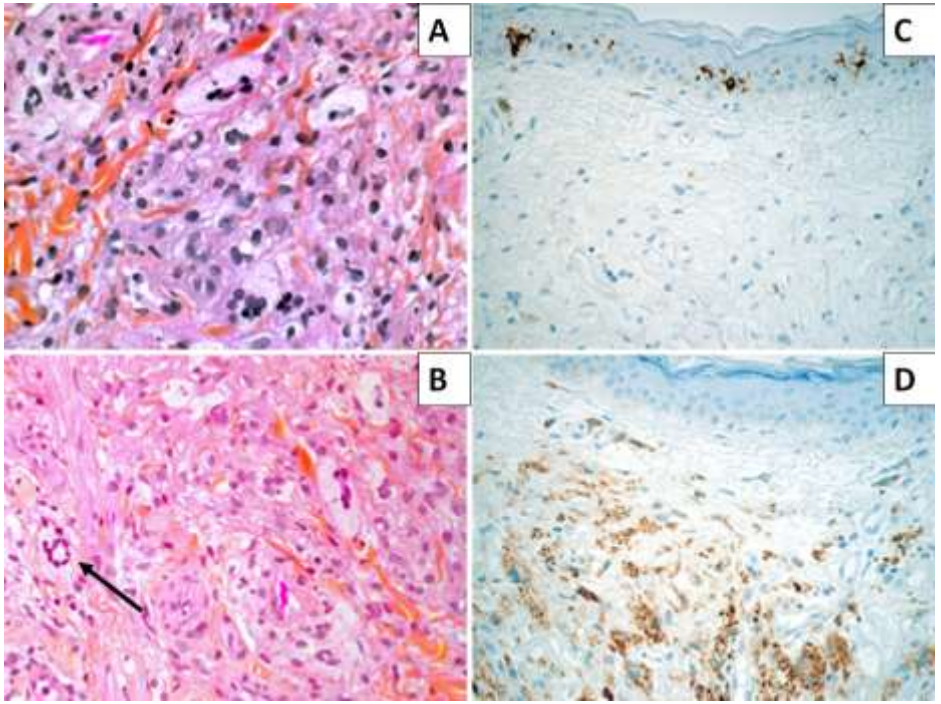


	All (n=120)	CH (n=51)	No CH (n=69)	p†
Sex (M/F)	82/38	38/13	44/25	0.24
Age at first symptoms (mean, SD)	53.12 (15.51)	59.39 (13.12)	48.48 (15.60)	<0.0001*
Age at diagnosis (mean, SD)	57.12 (13.88)	63.25 (10.80)	52.51 (14.21)	<0.0001*
Age at bone marrow aspirate (mean, SD)	61.58 (13.00)	67.00 (9.83)	58.00 (13.71)	<0.0001*
BRAF V600E	70/111 (63%)	36/49 (73%)	34/62 (55%)	0.049*
Mixed histiocytosis	20 (17%)	8 (16%)	12 (17%)	1.00
Long bone involvement	104 (87%)	42 (82%)	62 (90%)	0.28
Cardiac involvement	59 (49%)	27 (53%)	32 (46%)	0.46
Vascular involvement	67 (56%)	34 (67%)	33 (48%)	0.04*
Xanthelasma	24 (20%)	10 (20%)	14 (20%)	1.00
Diabetes insipidus	34 (28%)	11 (22%)	23 (33%)	0.22
CNS involvement	42 (35%)	15 (29%)	27 (39%)	0.33
Retro-orbital involvement	24 (20ù)	13 (25%)	11 (16%)	0.25
Retroperitoneal involvement	75 (63%)	38 (75%)	37 (54%)	0.02*
Myeloid malignancies	18 (15%)	16 (31%)	2 (3%)	<0.0001
Deaths	8 (7%)	4 (8%)	4 (6%)	0.72
Follow-up since diagnosis, months; mean (range)	59 (1 – 236)	52 (1 – 196)	59 (1 – 273)	0.39
Follow-up since bone marrow aspirate, months; mean (SD)	13.44 (4.46)	13.96 (4.83)	13.06 (4.16)	0.21
IFN-α or PEG-IFN-α	74 (62%)	31 (61%)	43 (62%)	1.00
Targeted therapy				
BRAF inhibitor	50 (42%)	28 (55%)	22 (33%)	0.02*
MEK inhibitor	21 (18%)	9 (18%)	12 (17%)	1.00

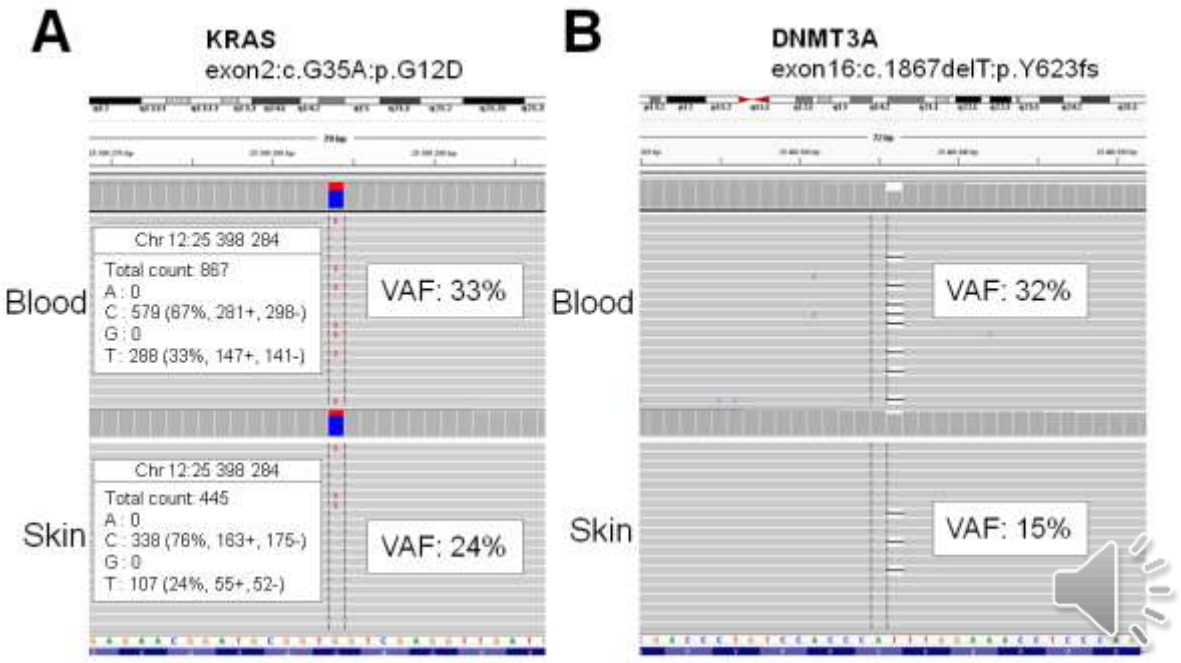
Papo M, Blood 2017
Cohen-Aubart Blood 2020

NGS 36 gènes moelle ECD : hématopoïèse clonale 42,5% des cas
TET2, *ASXL1*, *DNMT3A* *NRAS* mutations les plus retrouvées

+ LMMC

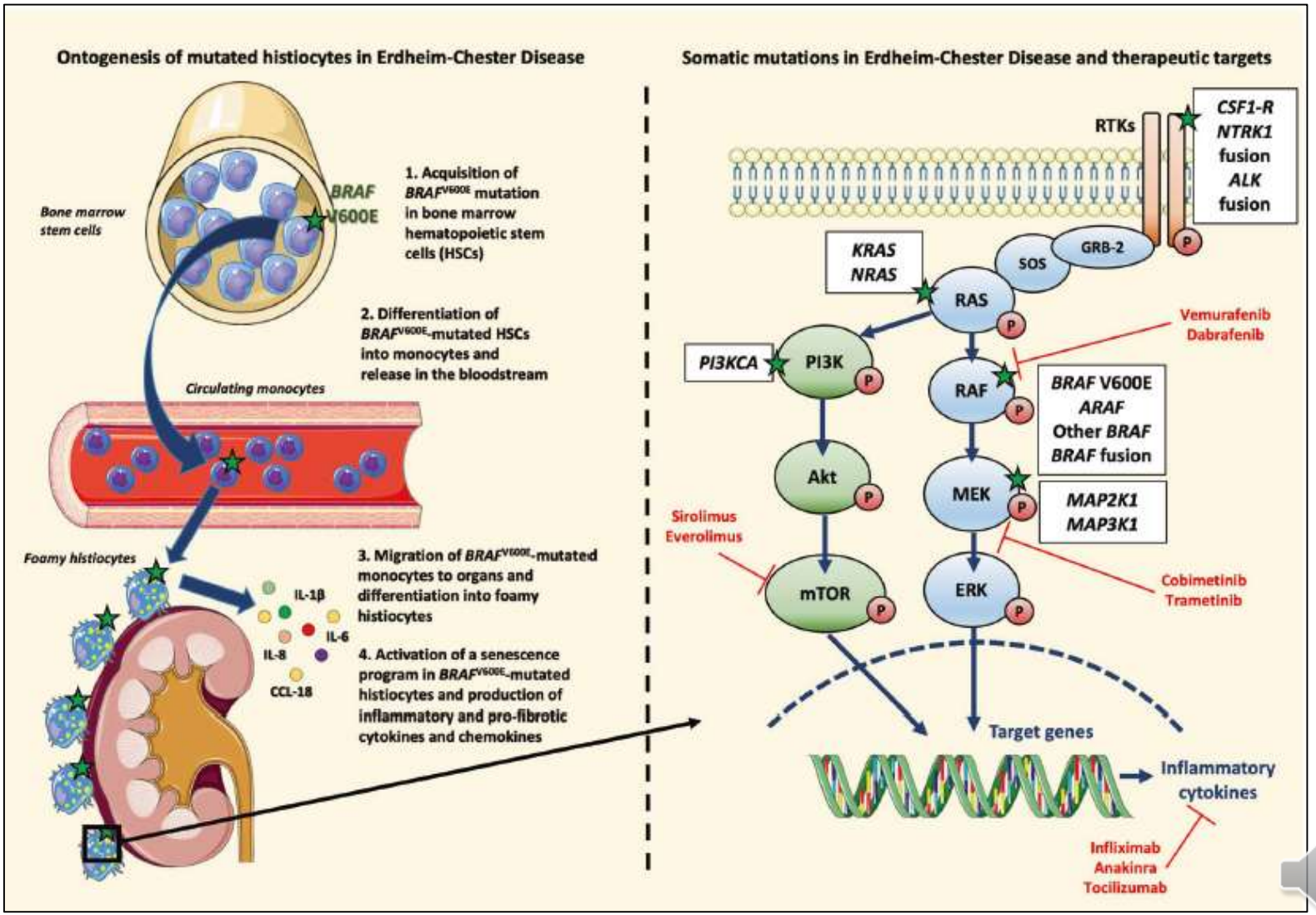


Critère de classification des ECD
Ou
Localisation cutanée LMMC



Bonnet, Haematologica 2020

Maladie d'Erdheim-Chester cibles thérapeutiques



Pegoraro Leukemia 2020

Maladie d'Erdheim-Chester

	Treatment	Recommendations
First-line therapy	Interferon alfa or pegylated interferon alfa	Best choice as front-line treatment of Erdheim-Chester disease; tolerance issues observed (fatigue, depression); pegylated form is better tolerated; this treatment is a major independent predictor of survival in Erdheim-Chester disease;[63] higher doses (9 million units given three times per week) recommended in cases with meningeal infiltration, subsellar and retrosellar masses, and pericardial and pseudo-atrial infiltration
Second-line therapy (or first-line therapy for life-threatening manifestations)	Vemurafenib and other BRAF inhibitors	Most impressive treatment responses seen if *BRAF*^{V600E} mutation is present (in 57–70% of patients) in multisystemic and refractory Erdheim-Chester disease despite interferon alfa therapy (eg, CNS and cardiovascular complications of Erdheim-Chester disease); safety issues (in particular, development of squamous-cell carcinoma); informed and signed consent mandatory; optimal length of treatment to be determined in future studies and in particular with the LOVE trial (NCT02089724); less effective in neurodegenerative Erdheim-Chester disease; vemurafenib accessible through the basket trial (NCT01524978) in the USA and the AcSé trial in France (NCT02304809)
Second-line therapy (or first-line therapy for life-threatening manifestations)	Cobimetinib and other MEK inhibitors alone or in combination	MEK inhibitors seem promising (perhaps even more so than BRAF inhibitors) in patients with wild-type BRAF; combination therapy (anti-BRAF plus anti-MEK) seems efficacious; a trial of combination therapy with trametinib plus dabrafenib (NCT02281760) is ongoing in the USA; the cobimetinib trial (NCT02649972) initiated for patients with wild-type *BRAF* or *BRAF*^{V600E} who are unable to take a BRAF inhibitor or have previously received treatment with a BRAF inhibitor that was discontinued because of intolerable side-effects or toxicity before disease progression is ongoing
Second-line therapy	Steroids	Usually not effective in Erdheim-Chester disease, except in severe exophthalmos or macrophage activation syndrome
Second-line therapy	Anakinra	Effective in mild Erdheim-Chester disease (bone pain, high concentrations of C-reactive protein); disappointing responses in severe cases with CNS and heart complications (eg, cardiac tamponade occurring with therapy)
Second-line therapy	Double autologous stem cell transplantation	Anecdotal efficacy was reported in 3 of 3 patients with Erdheim-Chester disease, but no improvement was seen in 2 of 3 patients[77]
Second-line therapy	Cladribine	Potential benefit observed in treatment of Erdheim-Chester disease with CNS involvement refractory to interferon alfa,[78] but unfavourable outcomes observed in unpublished small-scale studies at Pitié-Salpêtrière Hospital
Second-line therapy	Infliximab	Beneficial after 12–18 months in 2 of 2 patients with Erdheim-Chester disease with cardiac involvement; efficacy needs to be studied further[79]
Second-line therapy	Imatinib	Effective in three histiocytosis cases, but discouraging results seen in 6 of 6 patients with Erdheim-Chester disease in another study[80]
Second-line therapy	Sirolimus	Objective responses or disease stabilisation seen when combined with prednisone[75]

***Table 2*: Treatment recommendations for patients with Erdheim-Chester disease**

Haroche Lancet Oncol 2017

Erdheim-Chester disease: consensus recommendations for evaluation, diagnosis, and treatment in the molecular era

Gaurav Goyal,[1] Mark L. Heaney,[2] Matthew Collin,[3-5] Fleur Cohen-Aubart,[6] Augusto Vaglio,[7] Benjamin H. Durham,[8] Oshrat Hershkovitz-Rokah,[9,10] Michael Girschikofsky,[11] Eric D. Jacobsen,[12] Kazuhiro Toyama,[13] Aaron M. Goodman,[14] Paul Hendrie,[15] Xin-xin Cao,[16] Juvianee I. Estrada-Veras,[17] Ofer Shpilberg,[18,19] André Abdo,[20,21] Mineo Kurokawa,[13] Lorenzo Dagna,[22,23] Kenneth L. McClain,[24] Roei D. Mazor,[25] Jennifer Picarsic,[26] Filip Janku,[27] Ronald S. Go,[28] Julien Haroche,[29,*] and Eli L. Diamond[30,*]

Treatment	
Treatment is indicated for most ECD patients, except some select cases of asymptomatic minimal burden disease, which can be monitored closely	B
Systemic corticosteroids, surgery, and radiation therapy may be used to relieve edema or acute symptoms, but are not recommended as monotherapies for ECD	A
For patients with *BRAF-V600E* ECD who have cardiac/neurologic disease or end-organ dysfunction, BRAF-inhibitor therapy with vemurafenib or dabrafenib should be implemented as first-line therapy	A
For *BRAF-V600E* ECD without end-organ dysfunction, BRAF-inhibitors or conventional therapy may both be considered for first-line therapy based on toxicity profile and drug availability/experience of clinician	A
For ECD patients without BRAF-V600E and cardiac/neurologic disease or end-organ dysfunction, empiric treatment with MEK-inhibitor should be strongly considered as first-line therapy	A
Optimal duration and dosing of targeted therapies is not known, although relapse has been observed in the majority of cases following complete cessation of BRAF-inhibitors; maintenance treatment in the setting of metabolic remission with low-dose therapy as tolerated may be considered	A
For patients without access to targeted therapies and high-burden disease, IFN-α/PEG–IFN-α or cladribine therapy may be considered	A
For patients with low-burden disease involving bones and retroperitoneum, cytokine-directed therapy such as anakinra may be appropriate first-line therapy	B

Goyal Blood 2020

Maladie d'erdheim-chester anti-BRAF anti-MEK

Table 1. Clinical characteristics of treated patients

	Vemurafenib* (n = 50) or dabrafenib (n = 1)	Cobimetinib (n = 15)
Sex	15 females and 36 males	3 females and 12 males
Age at diagnosis, median (range), y	57 (17-72)	56 (34-71)
BRAF^{V600E}	49 (96)	10† (67)
BRAF WT	2† (4)	5 (33)
Mixed histiocytosis (ECD + LCH)	15 (29)	5 (33)
CNS	26 (51)	9 (60)
Cerebellar	15 (29)	7 (47)
Lung	18 (35)	6 (40)
Vascular	39 (76)	12 (80)
Heart	38 (75)	10 (67)
Xanthelasma	19 (37)	3 (20)
Diabetes insipidus	23 (45)	5 (33)
Retroperitoneal fibrosis	33 (65)	11 (73)
Bones	44 (86)	13 (87)
Previous treatments		
Anakinra	6 (12)	2 (13)
Interferon-α	36 (71)	11 (73)
Deaths	5 (10)	0
Targeted treatments‡		
Vemurafenib/dabrafenib, n	51	12
Cobimetinib, n	12	15

VEMURAFENIB 480 x2/j
COBIMETINIB 40mg/j 21j/28

Taux de réponse sur TEP-TDM 90%
75% de rechute à l'arrêt +++

Anti-MEK efficaces chez BRAF -

Cohen-Aubart F Blood 2017, Diamond EL, Nature 2019