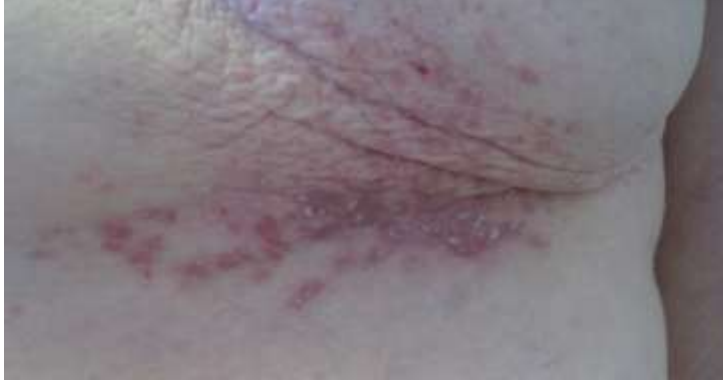


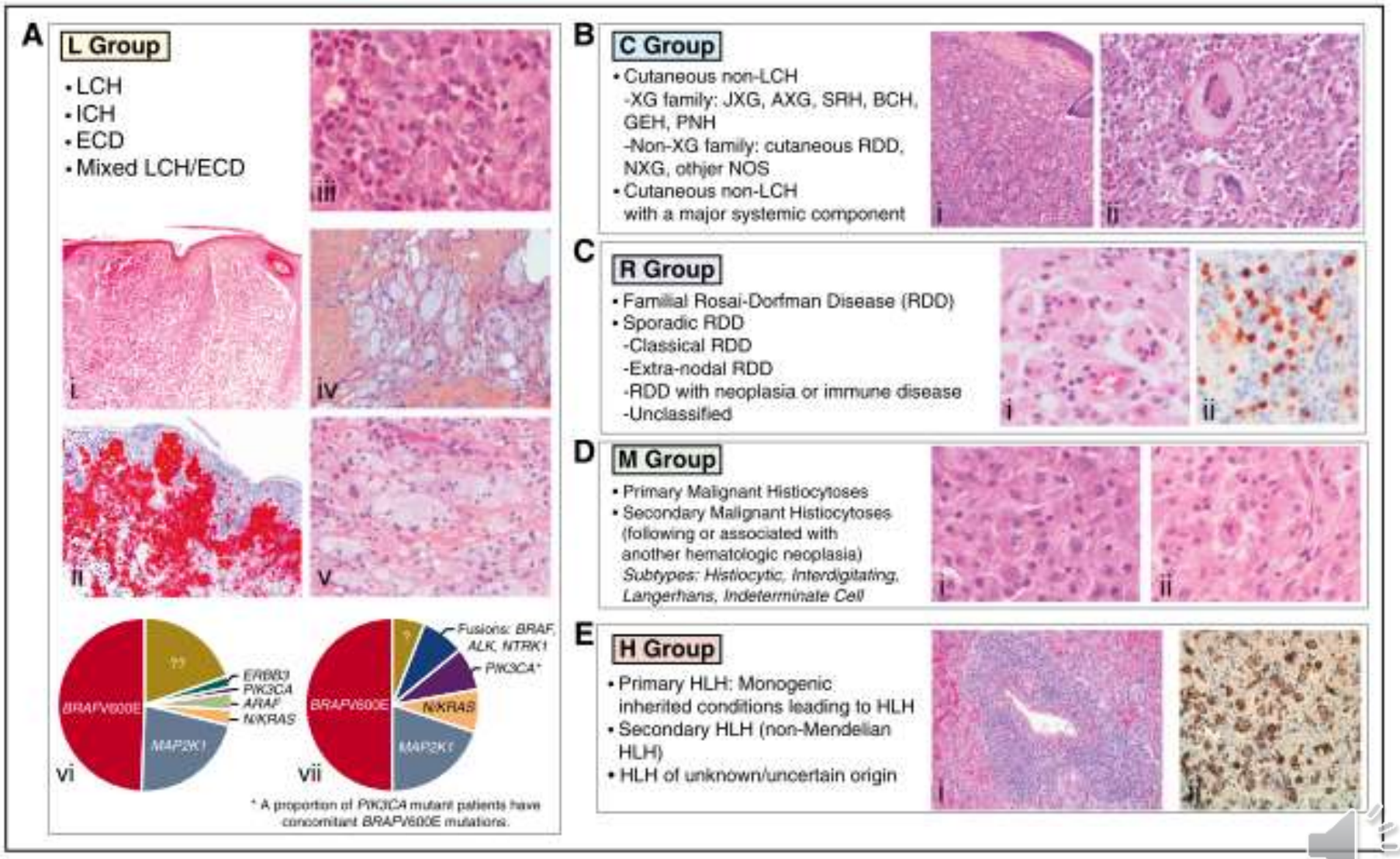
Manifestations cutanées des histiocytoses (groupes C et R)

François CHASSET

MCU-PH

Service de dermatologie et allergologie
hôpital Tenon

Classification des histiocytoses

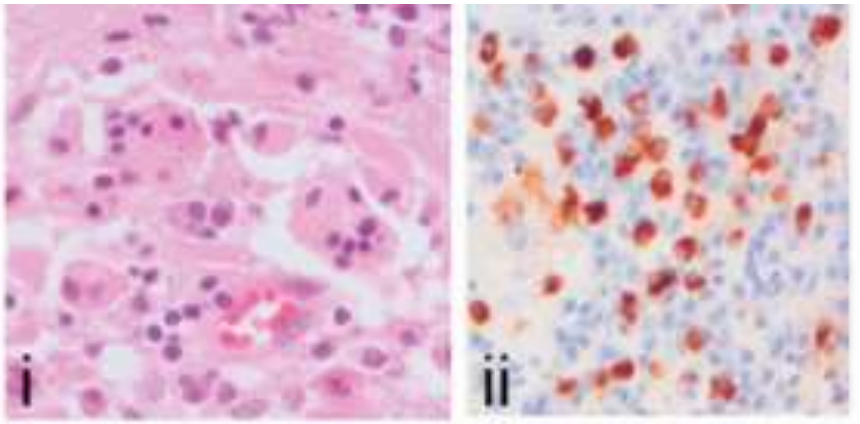


Emile, Blood 2016

Maladie de Rosai-Dorfman

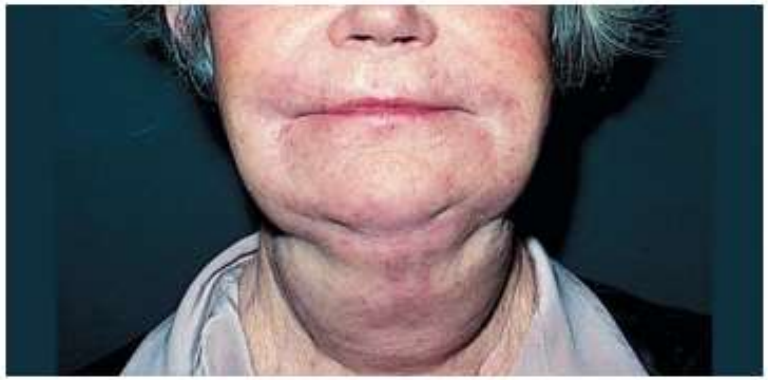
R Group

- Familial Rosai-Dorfman Disease (RDD)
- Sporadic RDD
  - -Classical RDD
  - -Extra-nodal RDD
  - -RDD with neoplasia or immune disease
  - -Unclassified



Emile Blood 2016

Maladie de Rosai-Dorfman

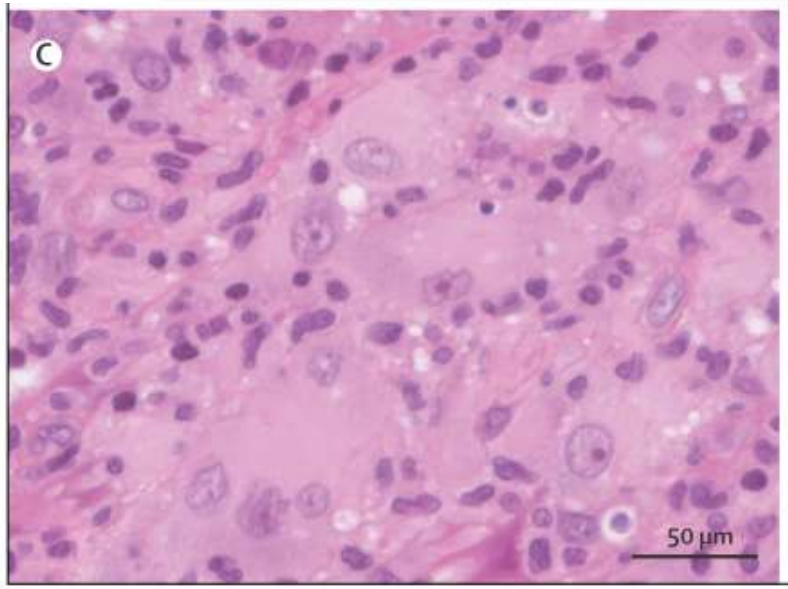


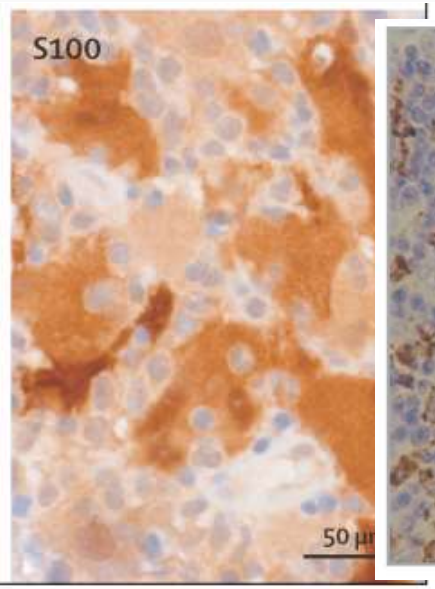
Atteinte cutanée et ganglionnaire

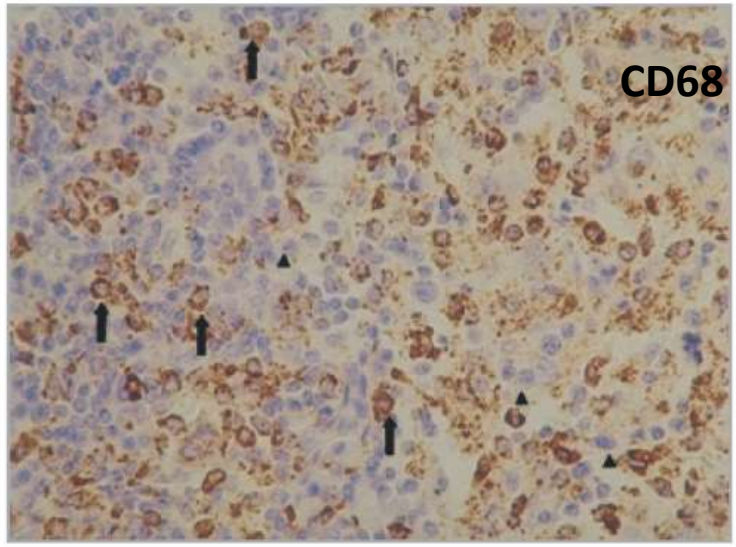
- Tableau classique:
  - Fièvre, AEG, amaigrissement, sueurs nocturnes
  - Adénopathies cervicales ++
  - Enfants, jeunes adultes
  - Origines Africaines ++
  - Atteinte cutanée 43%

Saurat 2017, Rosai 1972

Maladie de Rosai-Dorfman



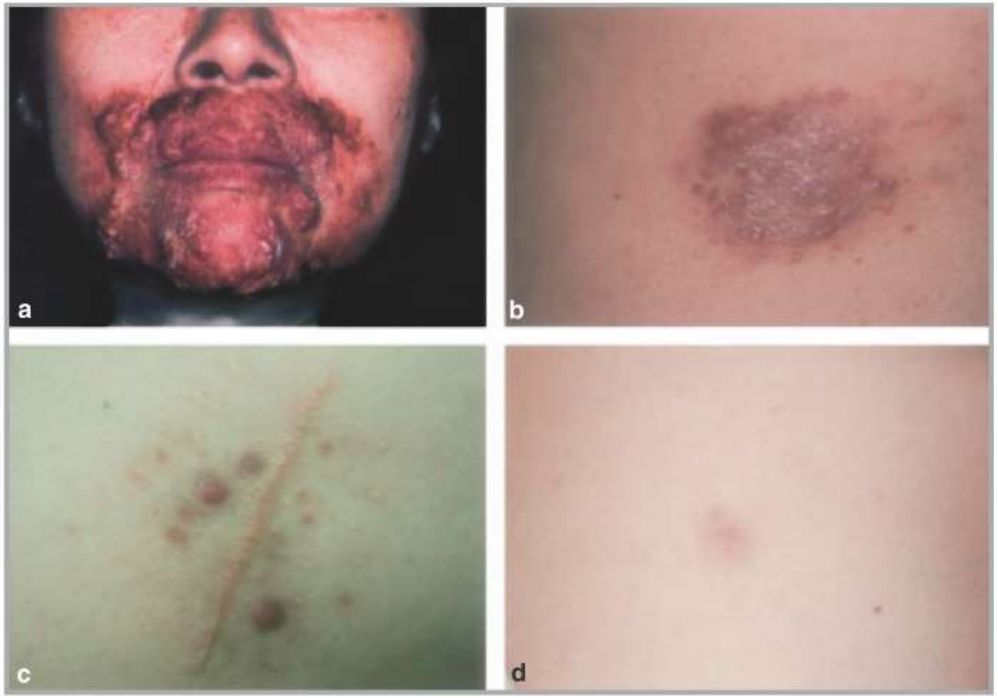




- RD cells: cytoplasme abondant , bord indistinct, grand noyau avec nucléole important
- CD68+, S-100+, CD1a-
- Empéripolèse ++ (lymphocytes au sein des histiocytes)
- Diagnostic parfois difficile si uniquement cutané: granulome annulaire, pseudo-tumeur

Wang BJD 2006

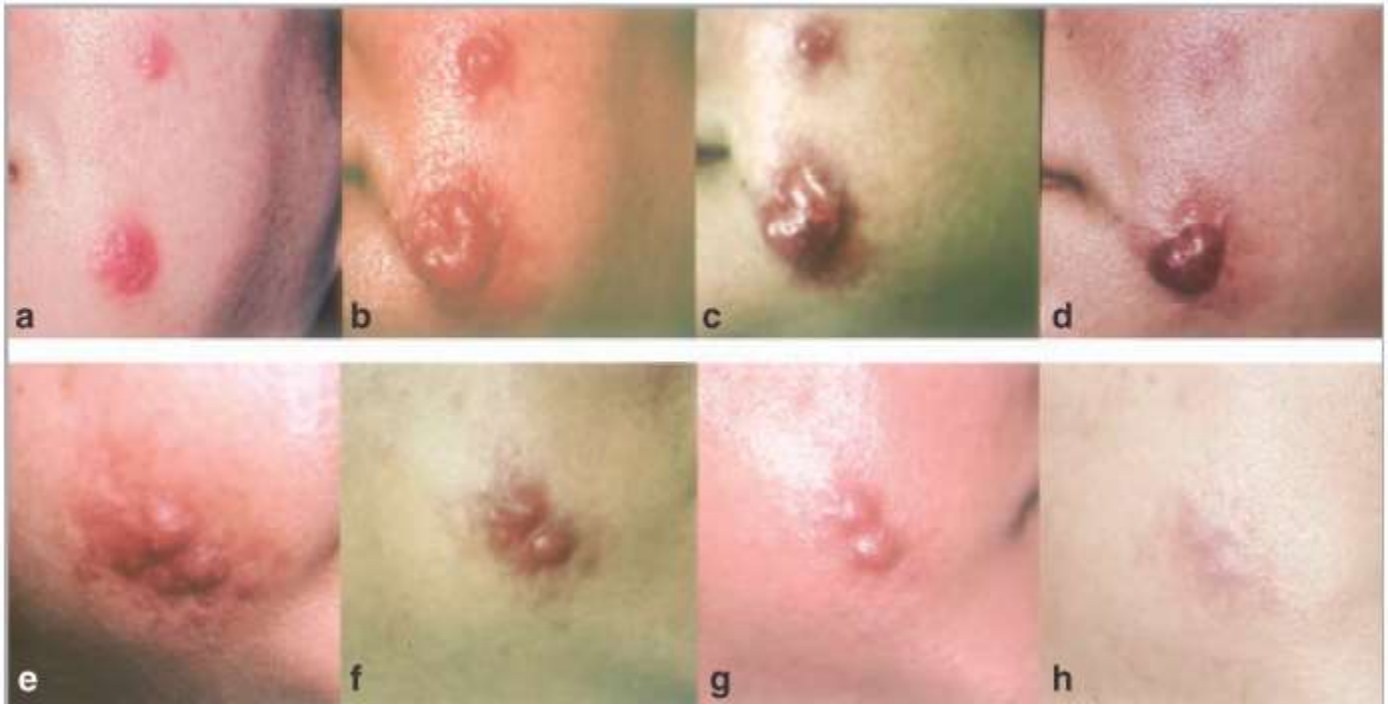
Maladie de Rosai-Dorfman



- Atteinte cutané atteinte extra-ganglionnaire la plus fréquente
- Atteinte visage ++
- Lésions polymorphes
- Nodules, plaques
- Couleur brune ++

Wang BJD 2006

Maladie de Rosai-Dorfman



Wang BJD 2006

Maladie de Rosai-Dorfman

Attributes		No. (%)	No. (%)	Clinical lesional types	of lesion at biopsy (months)
Epidermal changes		16 (76%)	Erosion/crusting 3 (14%)		10
			Acanthosis 3 (14%)		11
			Hypermelanosis 3 (14%)		6
			Attenuation of rete ridges 7 (33%)		17
Type of main infiltrate	Nodular/diffuse	16 (76%)	15 (71%)	Nodules/papules 9; plaques 6	15
			Nodular + xanthoma 1 (5%)	Nodule 1	30
	Patchy/interstitial	4 (19%)		Plaques 3; patches 1	7
	Suppurative granuloma	1 (5%)		Nodule 1	6
Cells	RD cells	20 (95%)	Few 4 (19%)		11
			Moderate 11 (52%)		11
			Many 5 (24%)		13
	Plasma cells	21 (100%)	Rare 1 (5%)		24
			Few 2 (10%)		4
			Many 18 (86%)		12
	Neutrophils	9 (43%)	Rare 1 (5%)		8
			Few 5 (24%)		8
			Many 3 (14%)		10
			Absent 12 (57%)		14
	Eosinophils	13 (62%)	Rare 4 (19%)		6
			Few 9 (43%)		17
			Absent 8 (38%)		9
	Foam cell	2 (10%)			24
Other features	Increased vascularity	19 (90%)	Present 19 (90%)		10
			Absent 2 (10%)		25
	Fibrosis	10 (48%)	Present 10 (48%)		16
			Absent 11 (52%)		6

All parameters were evaluated in haematoxylin and eosin-stained sections except Rosai–Dorfman cells (RD cells), in which S-100-stained sections were used. The numbers of RD cells were scored in a 40 × objective and the most populated focus was selected: few, < 10; moderate,

Maladie de Rosai-Dorfman

Une maladie mal comprise

Table 4. Histiocytoses of the R group

Histiocytoses of the R group
Familial RDD
Faisalabad (or H) syndrome (OMIM #602782)
FAS deficiency or ALPS-related RDD (OMIM #601859)
Familial RDD not otherwise specified
Classical (nodal) RDD
Without IgG4 syndrome
IgG4 associated
Extranodal RDD
Bone RDD
CNS RDD without IgG4 syndrome
CNS RDD, IgG4 associated
Single-organ RDD other than lymph node, skin, and CNS, without IgG4 syndrome
Single-organ RDD other than lymph node, skin, and CNS, IgG4 associated
Disseminated RDD
Neoplasia-associated RDD
RDD postleukemia
RDD postlymphoma
RDD associated with MH
RDD associated with LCH or ECD
Immune disease-associated RDD
SLE related
IJA related
AIHA associated
HIV associated
Other non-C non-L non-M non-H histiocytoses

AIHA, autoimmune hemolytic anemia; IJA, idiopathic juvenile arthritis; OMIM, Online Mendelian Inheritance in Man.

Formes familiales

Formes classiques ganglionnaires
Avec ou sans hyper IgG4

Formes extra-ganglionnaires:
Cutanées ++, osseuses, CNS, disséminées

Formes associées à une hémopathie

Formes associées à MAI:
Lupus systémique, AHAI +++ (10-15%)

Formes avec mutations MAPK

Emile, Blood 2016

Maladie de Rosai-Dorfman

Mutations in *SLC29A3*, Encoding an Equilibrative Nucleoside Transporter ENT3, Cause a Familial Histiocytosis Syndrome (Faisalabad Histiocytosis) and Familial Rosai-Dorfman Disease

Clinical diagnosis	Faisalabad histiocytosis	Familial SHML	Familial Rosai Dorfman disease/Faisalabad histiocytosis	H syndrome	Pigmented hypertrichosis with insulin dependent diabetes mellitus syndrome
SLC29A3 mutations	c.300+1G>A	p.Gly437Argp. Phe103X	p.Gly437Arg	p.Gly427Ser p.Gly437Arg p.Leu349SerfsX56	p.Met116Arg; p.Tyr314ThrfsX91 p.Gly437Arg; p.Glu444X p.Thr449Arg

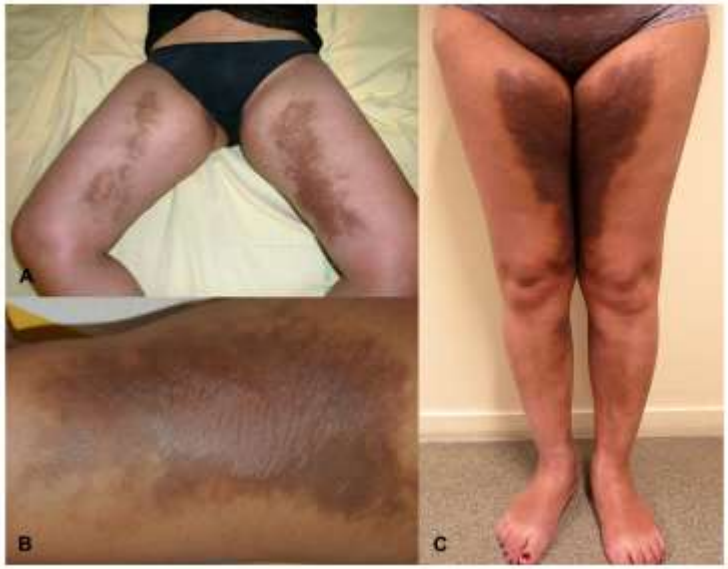
Tableaux cliniques associant: hyperpigmentation cutanée, surdité, retard de croissance, diabète, déformation des articulations, atteinte ganglionnaire avec parfois histologie de RDD

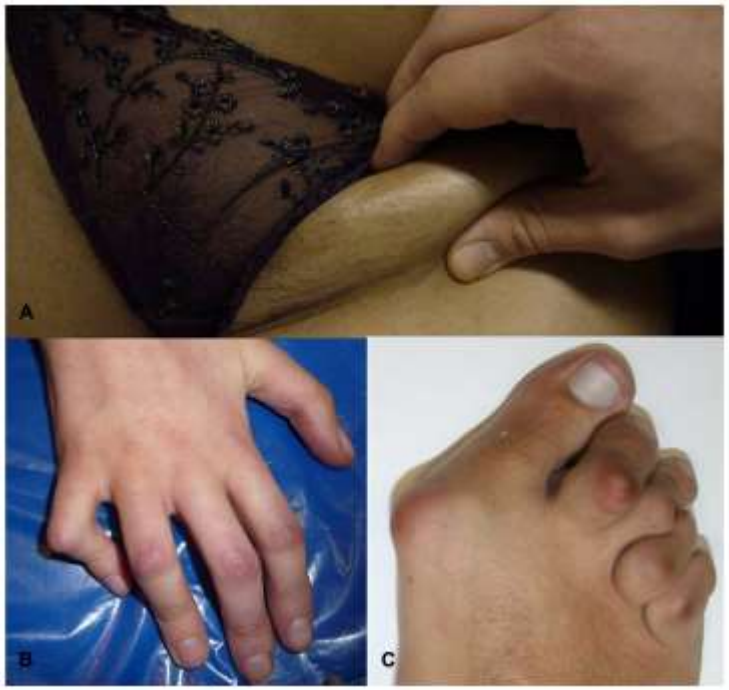
Morgan Plos Genetic 2010

Maladie de Rosai-Dorfman

H syndrome: The first 79 patients

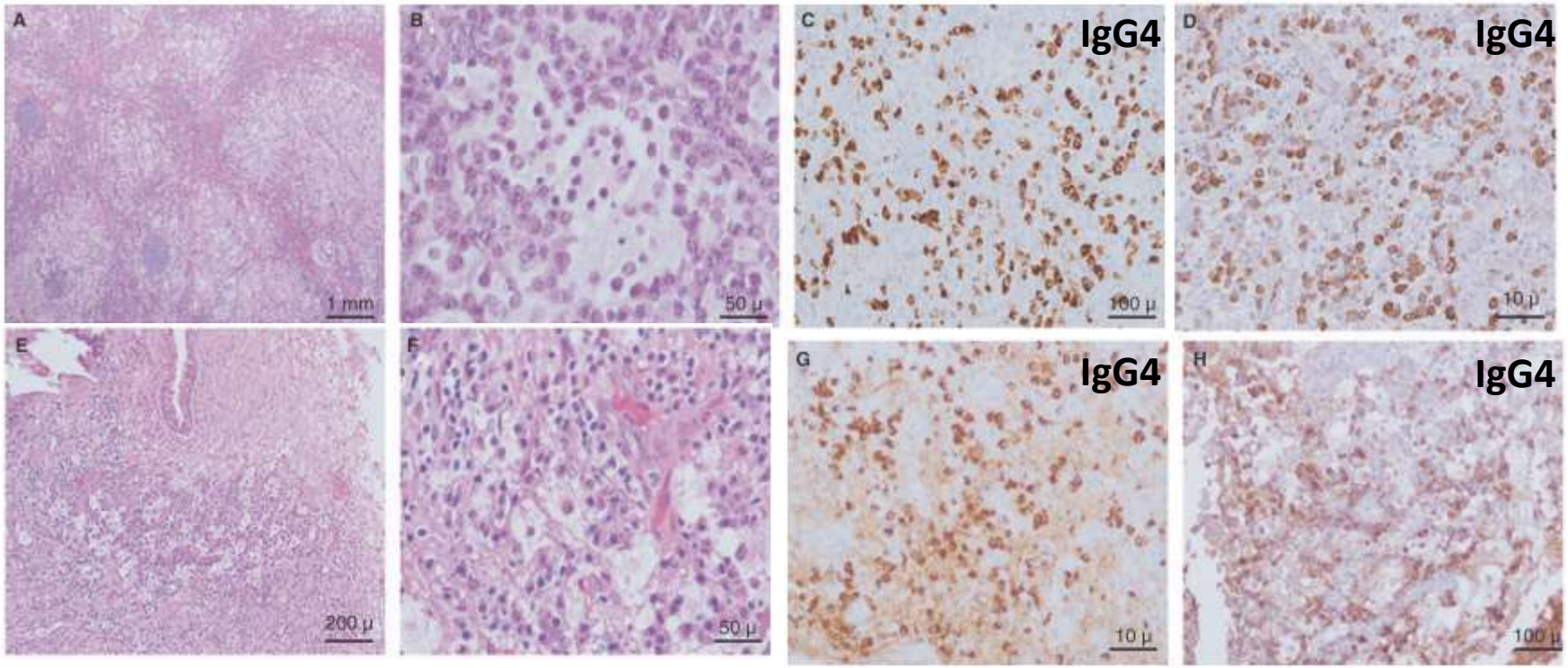
Vered Molho-Pessach, MD,[a,b] Yuval Ramot, MD, MSc,[a,b] Frances Camille, MD,[c] Victoria Doviner, MD,[d] Sofia Babay, BSc,[b] Siekavizza Juan Luis, MD,[e] Valentina Broshtilova, MD,[f] and Abraham Zlotogorski, MD[a,b]
Jerusalem, Israel; Paris, France; Guatemala City, Guatemala; and Sofia, Bulgaria





JAAD 2014

Maladie de Rosai-Dorfman et IgG4



12 /70 (17%) cas de RDD: plasmocytes IgG4/IgG > 40% dont 11 avec plasmocytes IgG4 > 200/HPF

Prédominance H > F 3:1 et âge > 55 ans vs 27 dans cas RDD IgG4+

Pas de différence d'atteinte d'organe ganglionnaire vs extra-ganglionnaire

Menon Histopathology 2014

Maladie de Rosai-Dorfman et mutations MAPK

Mutually exclusive recurrent *KRAS* and *MAP2K1* mutations in Rosai–Dorfman disease

Table 2 Comparison of clinicopathologic features of patients with or without *KRAS* and *MAP2K1* mutations

	Total	KRAS *or* MAP2K1-*mutated*	*Unmutated*	P-*value*
Number	21	7 (33%)	14 (67%)	
Age (years)[a]	43 (3–82)	10 (3–64)	53 (4–82)	0.0347
No. of pediatric patients	5 (24%)	4 (57%)	1 (7%)	0.0251
Gender				1.0000
Male	8 (38%)	3 (43%)	5 (36%)	
Female	13 (62%)	4 (57%)	9 (64%)	
Location, n *(%)*				
Head and neck	7 (33%)	6 (86%)	1 (7%)	0.0009
Nodal	5 (24%)	1 (14%)	4 (29%)	0.0244
Extranodal	13 (62%)	3 (43%)	10 (71%)	0.3972
Both	3 (14%)	3 (43%)	0 (0%)	0.0263
Stage, n *(%)*				0.0256
Unifocal	8 (50%)	0 (0%)	8 (73%)	
Multifocal	8 (50%)	5 (100%)	3 (27%)	
Data not available	5	2	3	
Follow-up (months)[a]	84 (7-352)	74 (7–352)	94 (16–154)	
Outcome, n *(%)*				1.0000
Clinical remission	7 (70%)	4 (80%)	3 (60%)	
Persistent disease	3 (30%)	1 (20%)	2 (40%)	
Data not available	11	2	9	

Garces Modern Pathol 2017

Ttt Maladie de Rosai-Dorfman

First-line therapy	
Observation ("wait and see")	Suitable for patients with uncomplicated lymph node; starting therapy mainly for cosmetic reasons is not recommended; colchicine may be given to prevent amyloidosis
Steroids	Suitable for patients with high fevers, tracheal compression, or vital organ compromise (bulky); effective in autoimmune-related Rosai-Dorfman disease and in bone, CNS, and orbital disease; once therapy is discontinued, monitor closely for recurrence
Surgery	Suitable for patients with resectable intracranial lesions, orbital Rosai-Dorfman disease or vital (bulky) organ compression (with or without steroids)
Sirolimus	Reasonable choice for ALPS-related Rosai-Dorfman disease, although no reports have been published yet
Second-line therapy	
Radiotherapy	Has limited efficacy, but one report showed benefit in refractory orbital Rosai-Dorfman disease; should be tried only if surgery is not feasible
Cladribine	Suitable for patients with relapsed disease, multisystem, non-resectable CNS or autoimmune-related Rosai-Dorfman disease
Clofarabine	Suitable for patients with relapsed disease, multisystem, non-resectable CNS or autoimmune-related Rosai-Dorfman disease
Imatinib	Suitable for patients with refractory or relapsed disease; mainly PDGFR-positive cases, but could work in any refractory Rosai-Dorfman disease although unlikely to be effective in all patients; may be more effective in less severe disease
Rituximab	Suitable for patients with refractory Rosai-Dorfman disease, autoimmune related (systemic lupus erythematosus)
Azathioprine	Anecdotal reports of efficacy
Oral 6-mercaptopurine	Suitable for patients with multiple relapses or as a maintenance therapy after steroids
Methotrexate	Suitable for patients with multiple relapses or as a maintenance therapy after steroids
Interferon alfa	Two reports showed success in refractory Rosai-Dorfman disease
Thalidomide	Anecdotal complete remission reported

ALPS=autoimmune lymphoproliferative syndrome. PDGFR=platelet-derived growth factor receptor.

Haroche Lancet Oncol 2017

Histiocytose du groupe C

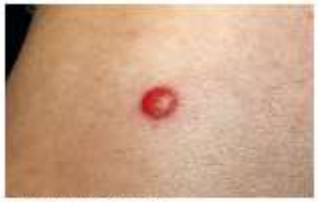
Table 2. Non-LCH of skin and mucosa (C group)

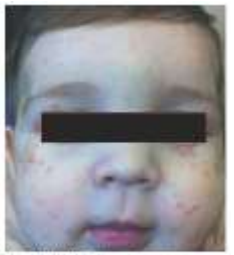
Non-LCH of skin and mucosa	
Cutaneous non-LCH histiocytoses	
XG family	JXG
	AXG
	SRH
	BCH
	GEH
	PNH
Non-XG family	Cutaneous RDD
	NXG
	Cutaneous histiocytoses not otherwise specified
Cutaneous non-LCH histiocytoses with a major systemic component	
XG family	XD
Non-XG family	MRH

AXG, adult xanthogranuloma; BCH, benign cephalic histiocytosis; GEH, generalized eruptive histiocytosis; JXG, juvenile xanthogranuloma; MRH, multicentric reticulohistiocytosis; NXG, necrobiotic xanthogranuloma; PNH, progressive nodular histiocytosis; RDD, Rosai-Dorfman disease; SRH, solitary reticulohistiocytoma; XD, xanthoma disseminatum; XG, xanthogranuloma.

Emile, Blood 2016

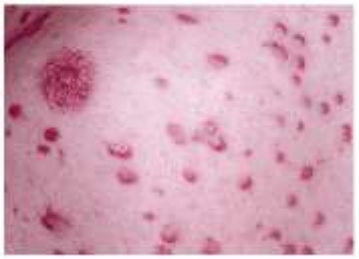
Famille xanthogranulome





- Juvenile xanthogranuloma
- Adult xanthogranuloma
- Solitary reticulohistiocytoma (XG avec anapath particulière)
- Benign cephalic histiocytosis

→ Formes le + souvent localisées

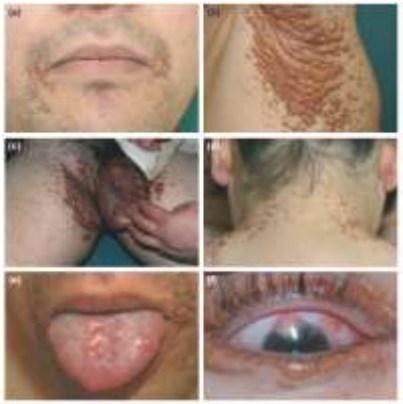


- Generelized eruptive histiocytosis
- Progressive nodular histiocytosis

→ Formes généralisées

- Xanthoma disseminatum

→ Forme généralisée avec atteinte systémique prédominante



Atteinte cutanée prédominante +++

Classification probablement incomplète ou redondante

Adult ou Juvenile xanthogranuloma avec mutation MAPK = histiocytose du groupe L

Histiocytose du groupe C

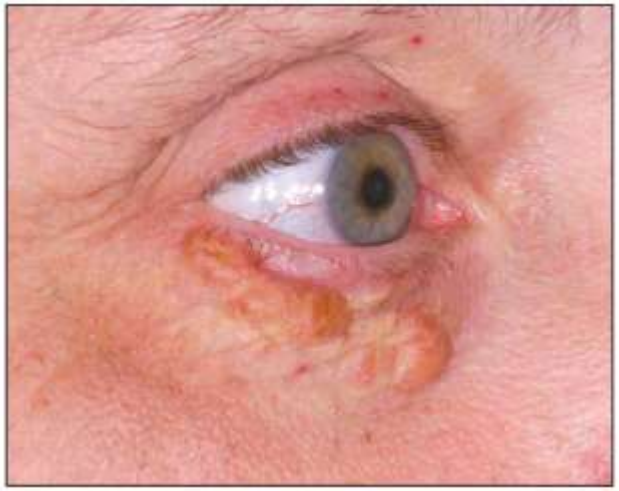
Table 2. Non-LCH of skin and mucosa (C group)

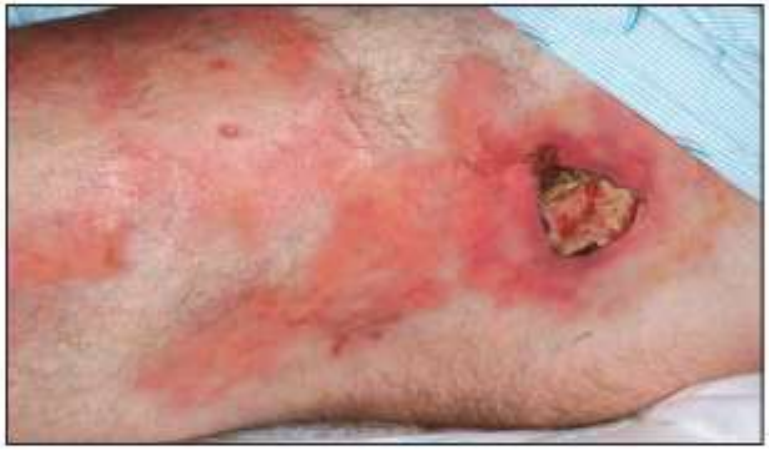
Non-LCH of skin and mucosa	
Cutaneous non-LCH histiocytoses	
XG family	JXG
	AXG
	SRH
	BCH
	GEH
	PNH
Non-XG family	Cutaneous RDD
	NXG
	Cutaneous histiocytoses not otherwise specified
Cutaneous non-LCH histiocytoses with a major systemic component	
XG family	XD
Non-XG family	MRH

AXG, adult xanthogranuloma; BCH, benign cephalic histiocytosis; GEH, generalized eruptive histiocytosis; JXG, juvenile xanthogranuloma; MRH, multicentric reticulohistiocytosis; NXG, necrobiotic xanthogranuloma; PNH, progressive nodular histiocytosis; RDD, Rosai-Dorfman disease; SRH, solitary reticulohistiocytoma; XD, xanthoma disseminatum; XG, xanthogranuloma.

Emile, Blood 2016

Xanthogranulome nécrobiotique





Wood, JAMA dermatol 2009

H=F, âge moyen 50 ans

Infiltré ++

Atrophie, télangiectasies +/-

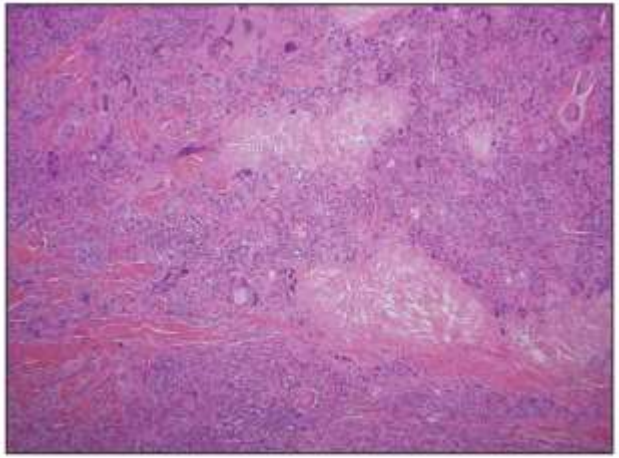
Topographie:

- Périorbitaire 65%
- Tronc 50%
- MI: rare

Caractère ulcéré: 50%

Gammapathie monoclonale ≈80% IgGκ>>λ , myélome rare

Xanthogranulome nécrobiotique



Pattern en bande d'inflammation granulomateuse +++

Rares pattern sarcoïdosique

Nécrobiose dans 100% des cas

Table. Clinical and Histopathologic Features of 12 Patients With Necrobiotic Xanthogranuloma

Sex/Age, y	Anatomic Site	Cholesterol Clefts	Atypical Giant Cells	Plasma Cell Grade[a]	Nodular Lymphocytes
M/64	R lower leg	Yes	Yes	2	Yes
M/35	R upper eyelid	No	No	1	Yes
M/76	Periorbital	Yes	Yes	3	Yes
M/82	L neck	No	Yes	1	Yes
	L upper arm	No	Yes	2	Yes
F/55	R upper eyelid	Yes	Yes	1	Yes
F/34	L flank	No	Yes	1	Yes
F/60	Chest	No	Yes	3	Yes
M/47	Forehead	No	No	2	Yes
	R forearm	No	No	1	Yes
M/26	Penis	No	Yes	1	Yes
M/28	L temple	No	Yes	3	Yes
M/45	L upper thigh	No	Yes	1	No
	L arm	No	Yes	1	Yes
F/53	L leg	Yes	Yes	2	Yes

Wood, JAMA dermatol 2009

Xanthogranulome nécrobiotique

Table 1. Demographics and Comorbidities of Necrobiotic Xanthogranuloma

Patient Characteristic	Patients, No./Total No. (%)		
	Multicenter Cohort (n = 34)	Systematic Review (n = 201)	Overall (n = 235)
Age, mean (SD), y	61.6 (14.1)	61.9 (14.2)	61.8 (14.2)[a]
Sex			
Female	23/34 (68)	124/201 (61.7)	147/235 (62.6)
Male	11/34 (32)	77/201 (38.3)	88/235 (37.4)
Race			
White	32/33 (97)	46/57 (81)[a]	78/90 (87)
Asian	0	11/57 (19)	11/90 (12)
Black or African American	1/33 (3)	0	1/90 (1)
Paraproteinemia	26/34 (76)[b]	167/201 (83.1)	193/235 (82.1)
IgG-κ	15/34 (44)	102/201 (50.7)	117/235 (50.0)
IgG-λ	8/34 (24)	41/201 (20.4)	49/235 (20.8)
IgM	1/34 (3)	4/201 (2.0)	5/235 (2.1)
IgA		2/201 (1.0)	2/235 (0.8)
Polyclonal	2/34 (6)	6/201 (3.0)	8/235 (3.4)
Unspecified type		12/201 (6.0)	12/235 (5.1)
Malignant condition	8/34 (24)[c]	51/201 (25.4)	59/235 (25.1)
Multiple myeloma	5/34 (15)	28/201 (13.9)	33/235 (14.0)
Lymphoma	2/34 (6)	13/201 (6.5)	15/235 (6.4)
Leukemia	1/34 (3)	7/201 (3.5)	8/235 (3.4)
Breast cancer	0	1/201 (0.5)	1/235 (0.4)
Rectal cancer	0	1/201 (0.5)	1/235 (0.4)
Waldenstrom macroglobulinemia	0	1/201 (0.5)	1/235 (0.4)

Méthode Delphi : non validés

Box. Diagnostic Criteria for Necrobiotic Xanthogranuloma[a]

Major Criteria

1. Cutaneous papules, plaques, and/or nodules, most often yellow or orange in color.
2. Histopathological features demonstrating palisading granulomas with lymphoplasmacytic infiltrate and zones of necrobiosis. Characteristic features that are variably present include cholesterol clefts and/or giant cells (Touton or foreign body).

Minor Criteria

1. Paraproteinemia, most often IgG-κ, plasma-cell dyscrasia, and/or other associated lymphoproliferative disorder.
2. Periorbital distribution of cutaneous lesions.

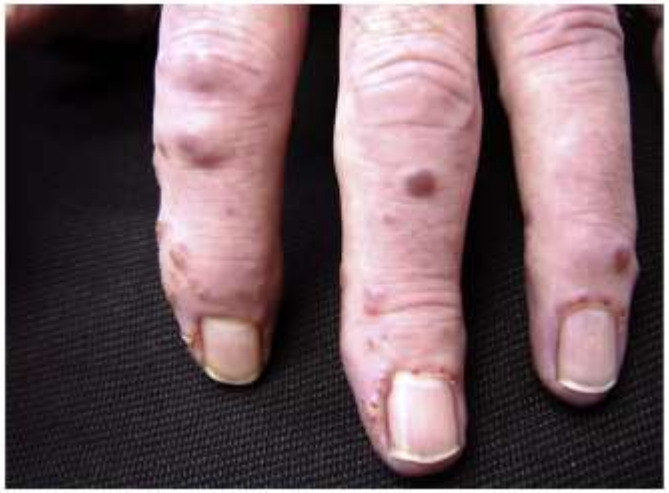
[a] Both major criteria and at least 1 minor criterion are required for diagnosis, applicable only in the absence of foreign body, infection, or other identifiable cause.

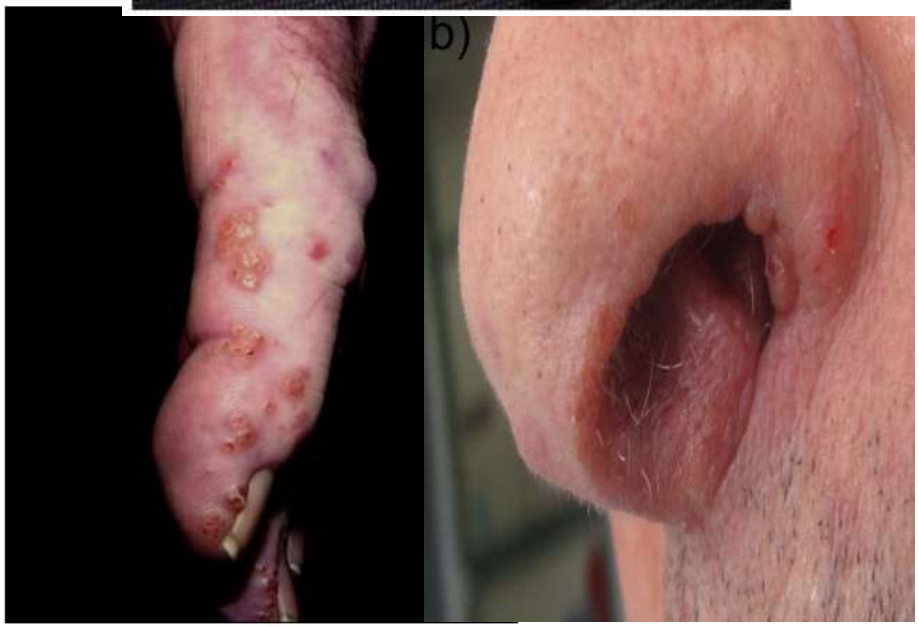
Table 3. Treatment Response for Necrobiotic Xanthogranuloma in the Multicenter Cohort

Treatment[a]	Response Rate, No./Total No. (%) (n = 34)
Intravenous immunoglobulin	9/9 (100)
Antimalarial	4/5 (80)
Intralesional triamcinolone	6/8 (75)
Surgery[b]	3/4 (75)
Chemotherapy (alkylating agents, antimetabolites, and/or proteasome inhibitors)	8/12 (67)
Lenalidomide or thalidomide	5/8 (63)

Nelson, JAMA dermatol 2020

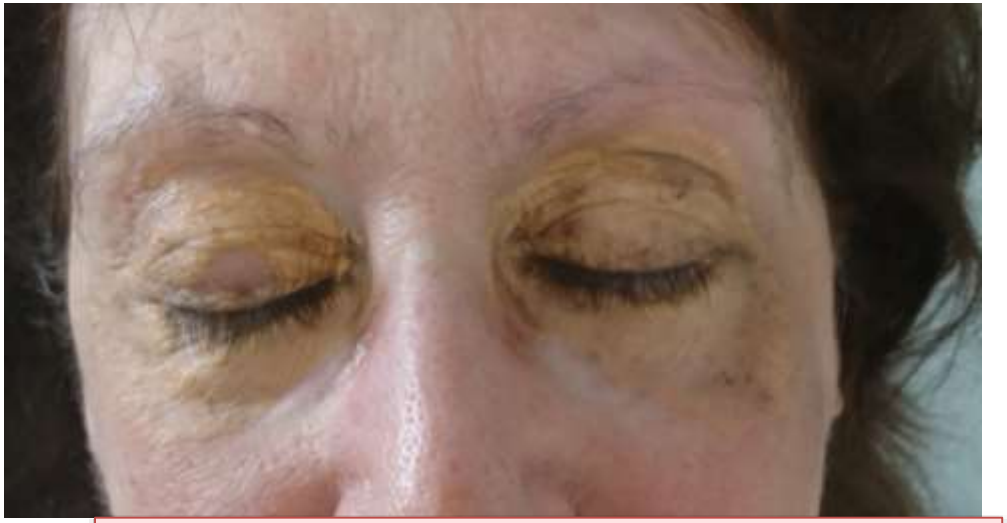
Réticulohistiocytose multicentrique





- Femme 50-60 ans
- Papules rouges, violacées mains ++
- Atteinte périunguéale évocatrice
- Xanthelasma, atteinte péri-narinaire ≈ 20%
- Associations: MAI, cancers ++
- Traitement: HCQ, MTX, Leflunomide

Démarche diagnostique Xanthélasma



Xanthelasma « classiques »

- FDRCV
- Dyslipidémie
- Peu étendus
- Limités canthus interne
- Pas de points d'appels

Xanthelasma-like lesion:

- Pas de dyslipidémie
- Extensif, circonférentiel
- Ulcération : xanthogranulome nécrobiotique
- Pathologie hémato: LMMC (ECD), gammapathie (Xanthogranulome nécrobiotique)
- Douleurs osseuses : ECD
- Si doute scinti os

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