Erdheim-Chester disease and Skin issues

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Introduction

- Erdheim-Chester (ECD) is an orphan disease included in the spectrum of systemic non-langerhans cell histiocytosis with frequent recurrent $BRAF^{V600E}$ mutation
- Recent data have been released for skin manifestations of ECD
- As many molecular targeted therapies (MTT) are currently used for patients with BRAF mutation, one might expect MTT toxicities including skin manifestations

Skin issues

- ECD skin manifestations
- ECD and MTT skin toxicities

ECD and skin manifestations

- Recently described ≃ 5 years
- Prevalence 19-28 % of ECD patients
- Various clinical manifestations
- First Series n=40 pts
  - *Chasset F, Barete S, Charlotte F et al JAAD. 2016;74:513-20*

Arnaud L et al Blood 2011, Haroche J et al Blood 2012, Haroche J et al Rheum Dis Clin North Am. 2013.

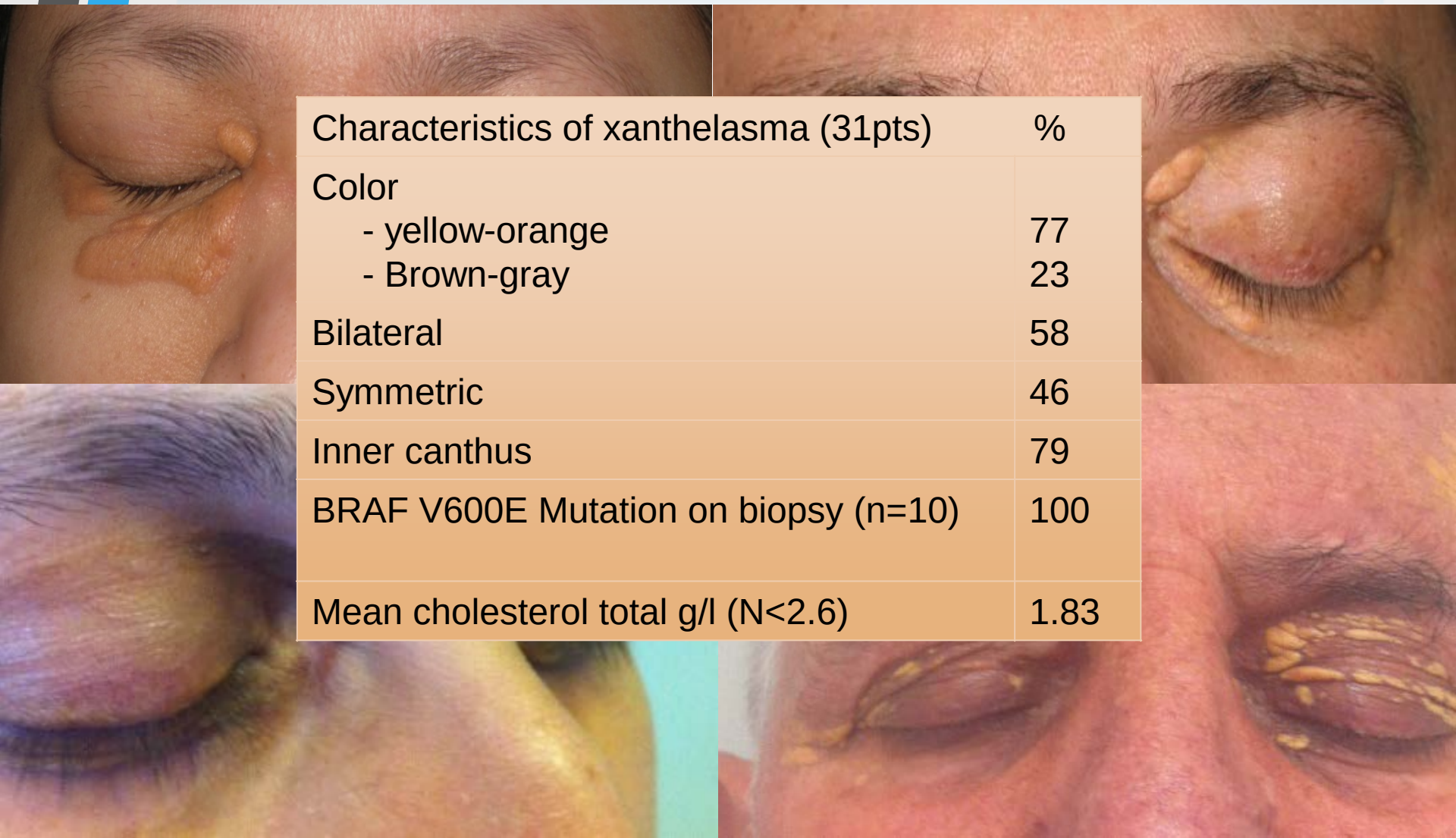
Patients and methods

- Retrospective study, 123 patients with ECD
- Aims:
  - Describe skin manifestations associated to ECD
  - Search for xanthelasma like lesions considered as specific
  - Search for others « histiocytes cells » lesions
  - Pathology analysis of skin samples
  - Case-control study for pathology on xantelasma like ECD and controls with classic xanthelasma with morphology and immunohistochemical parameters.
    - 7 cases compared each to 2 controls without ECD
  - BRAF status on skin biopsies

Results: ECD characteristics

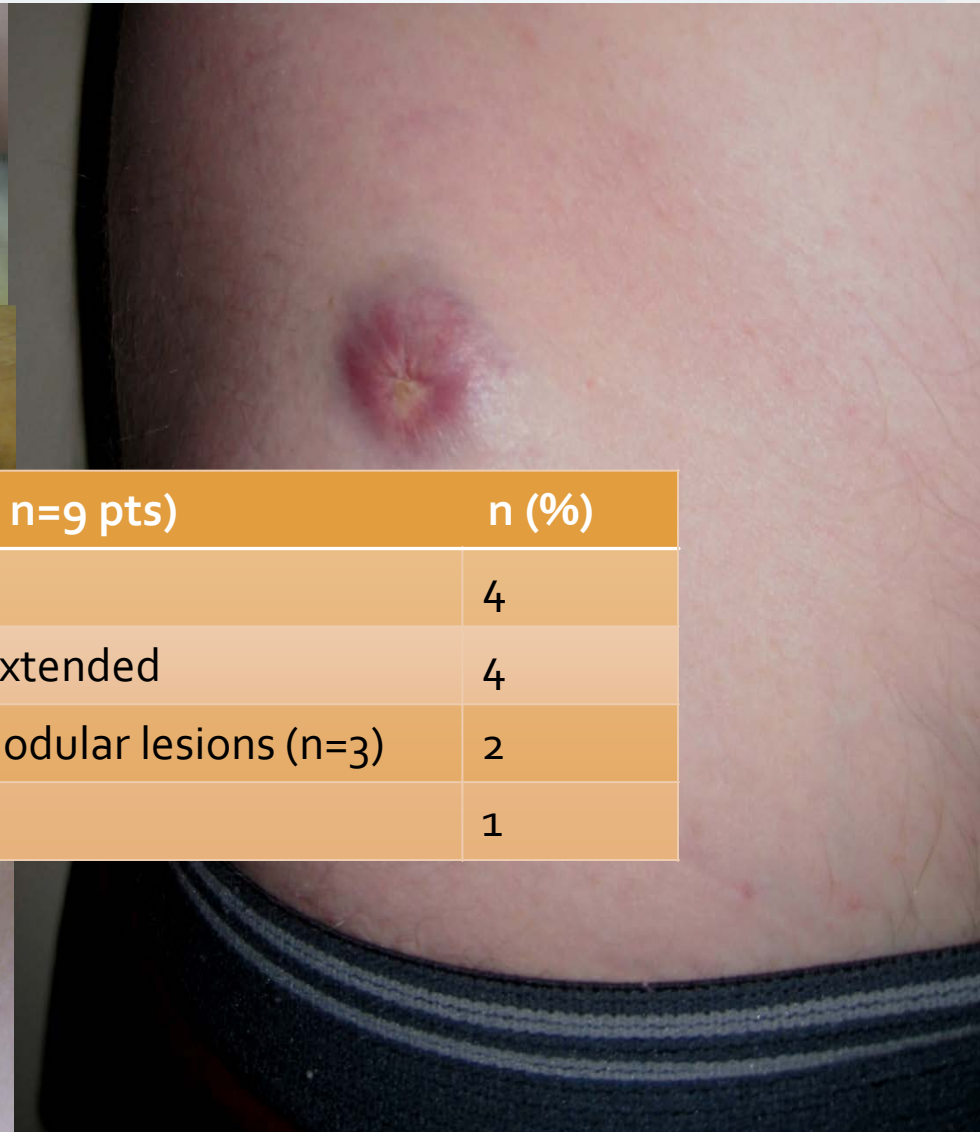
Variables	n (%)
ECD	31 (25)
ECD + Langerhans cells histiocytosis	9 (7)
Male sex	27 (67)
Median age at first symptom, y (range)	51 (23-80)
Median age at diagnosis, y (range)	54.5 (26-81)
Diagnostic delay, y (range)	3 (0-17)
Alive at last follow-up	33 (83)
First symptom	
Cutaneous	12 (30)
Xanthelasma-like lesions	10 (83)
Other lesions	2 (17)
Neurologic symptoms*	7 (18)
Bone pain	5 (12)
Diabetes insipidus	6 (15)
Respiratory symptoms†	4 (10)
Others‡	6 (15)
Site of the first biopsy	
Skin	15 (38)
Perirenal fat	14 (35)
Cerebral	3 (7)
Bone	2 (5)
Other§	6 (15)
Appearance of specific skin lesion before diagnosis	26 (79)
ECD diagnosed based on the skin lesion	14 (36)
BRAF^{V600E} status	
Positive	25 (76)
Negative	8 (24)
Noninformative sample or NA	7 (18)

Xanthelasma-like lesions



Characteristics of xanthelasma (31pts)	%
Color - yellow-orange - Brown-gray	 77 23
Bilateral	58
Symmetric	46
Inner canthus	79
BRAF V600E Mutation on biopsy (n=10)	100
Mean cholesterol total g/l (N<2.6)	1.83

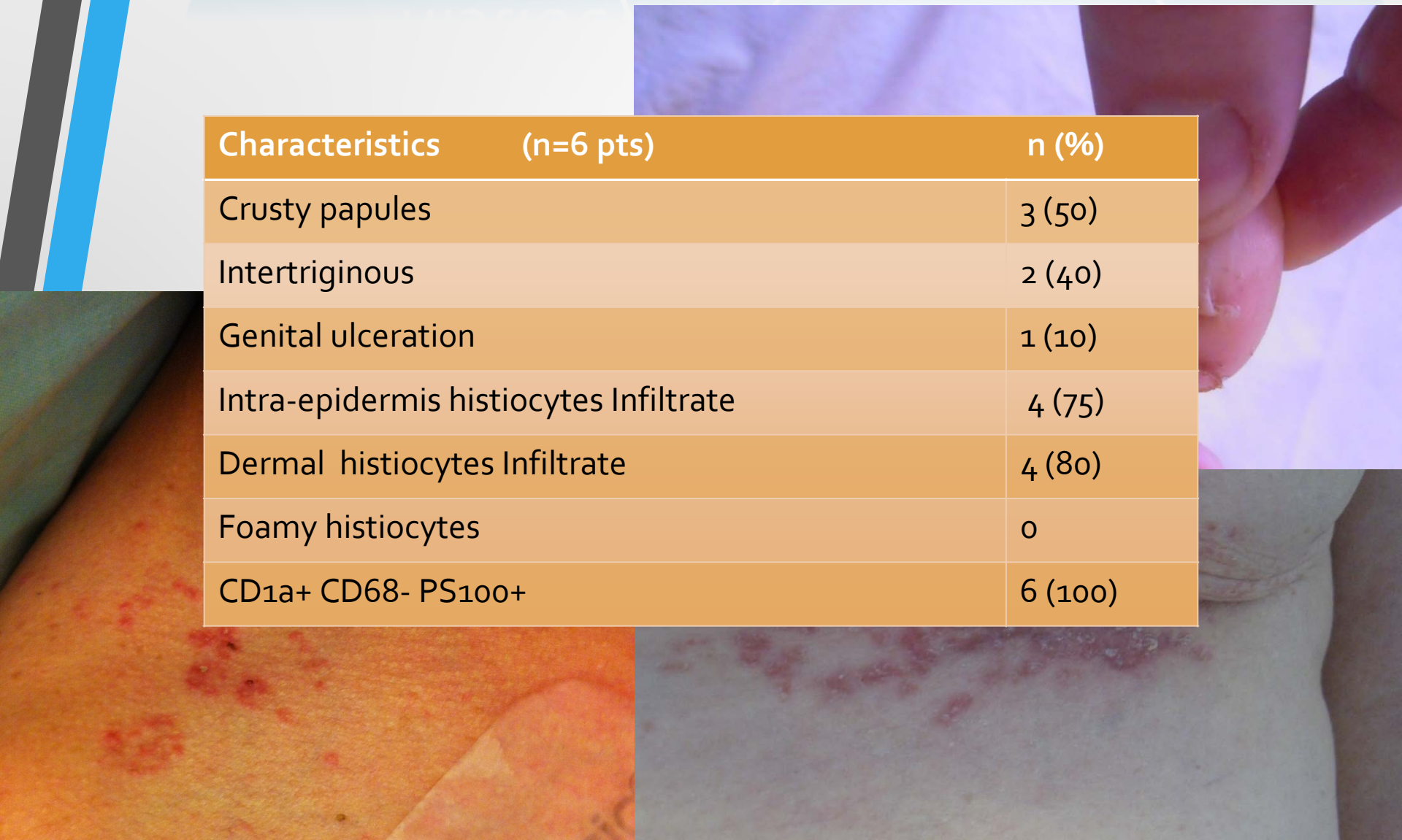
Others specific lesions of ECD



Characteristics of others lesions (n=9 pts)	n (%)
Papulo nodular lesions	4
Brown plaques or pigmented +/- extended	4
BRAF V600E mutation on papulo nodular lesions (n=3)	2
Genital ulceration	1

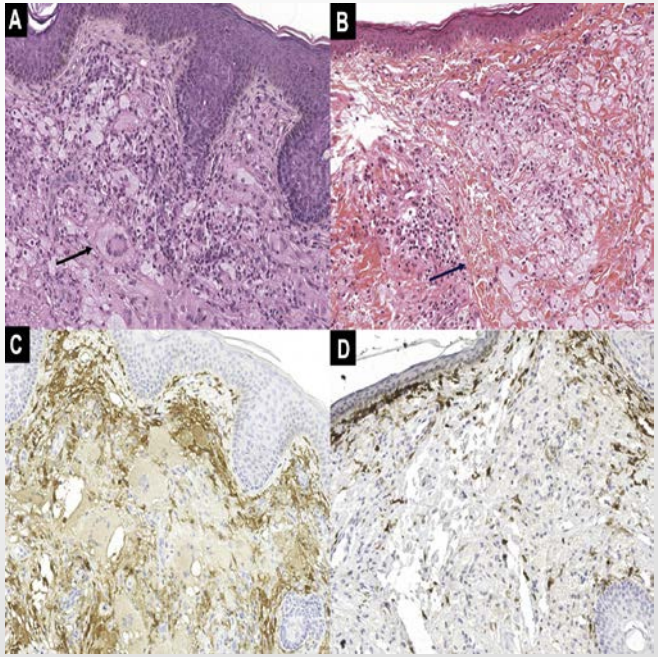
Associated langerhans cells histiocytes (mixed form)

Characteristics (n=6 pts)	n (%)
Crusty papules	3 (50)
Intertriginous	2 (40)
Genital ulceration	1 (10)
Intra-epidermis histiocytes Infiltrate	4 (75)
Dermal histiocytes Infiltrate	4 (80)
Foamy histiocytes	0
CD1a+ CD68- PS100+	6 (100)



Pathological comparison between ECD xanthelasma like lesions and classic xanthelasma

Features	ECD XLL	Classic xanthelasma	*P* value
Histiocyte infiltrate reaching more reticular dermis	3/7	0/14	.02
High density of multinucleated cells (score = 2)	3/7	0/14	.02
High density of Touton cells (score = 2)	5/7	1/14	.005*
High density of foamy cells (score = 2)	7/7	14/14	NS
Fibrosis	3/7	14/14	.005*
Immunostaining with $CD68^+$ >50% of the histiocytes	7/7	14/14	NS
Immunostaining with $CD163^+$ >50% of the histiocytes	7/7	14/14	NS
Immunostaining with S100 $protein^+$	1/7	2/14	NS
Immunostaining with $CD1a^+$	0/7	0/14	NS
Immunostaining with $FXIII^+$ >30% of the foamy cells	7/7	3/14	.001*

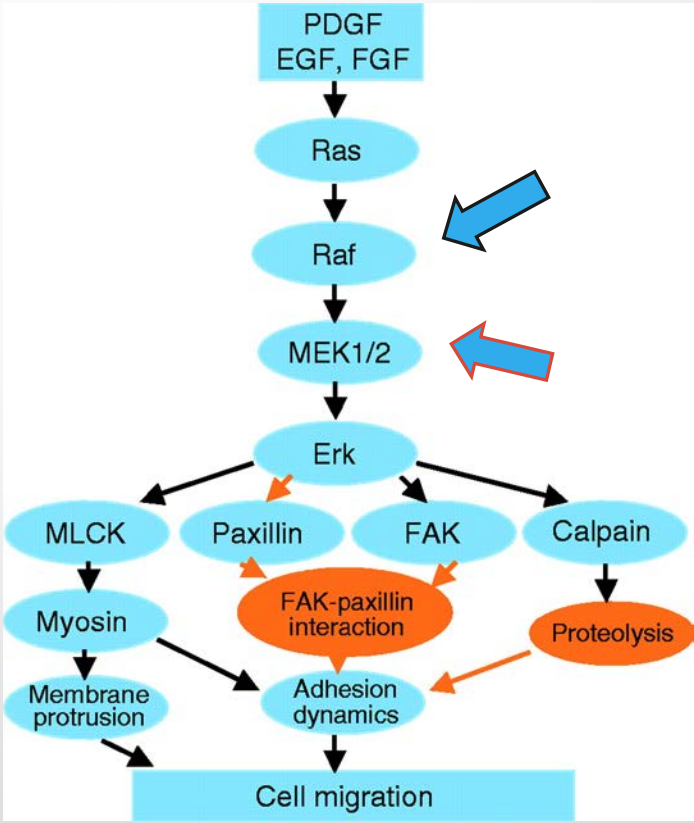


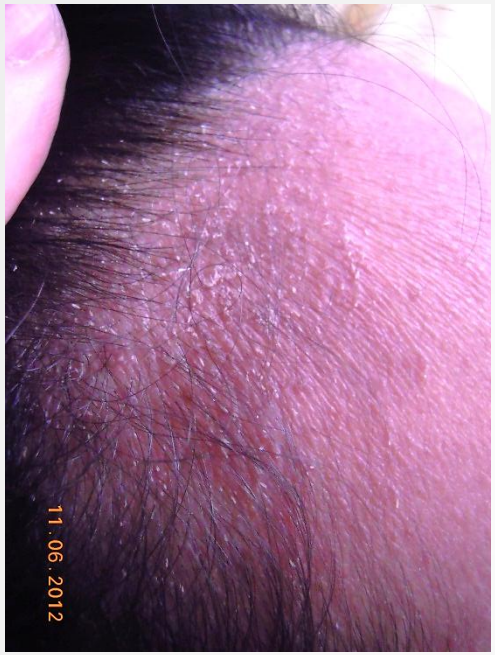
Take away messages

- First description of a series of ECD skin lesions: XLL is the most prevalent
- Pathology of XLL: interest of morphology and density of histiocytes cells infiltrate and touton cells for ECD diagnosis
- XLL biopsy is easy and usefull for mutational status (BRAF status) in a context of ECD

ECD and MTT skin toxicities

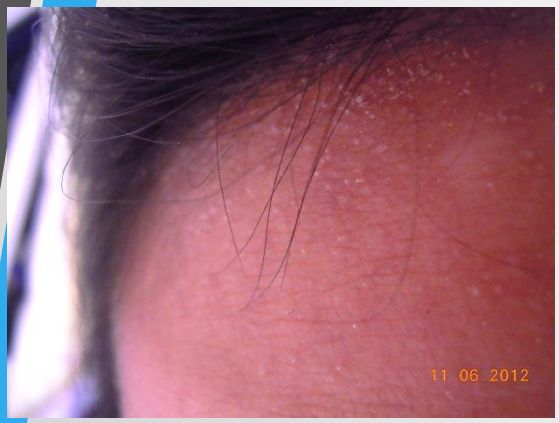
- Large developpement of MTT in metastatic melanoma with BRAF mutation has improved global knowledge about skin MTT toxicities
- MTT are required for ECD patients with BRAF mutation (>55%)
- Targets are kinases on MAPK pathway using:
  - BRAF inhibitor (vemurafenib/dabrafenib)
  - MEK inhibitor (cobimetinib/trabetinib)
  - Combinations of KI

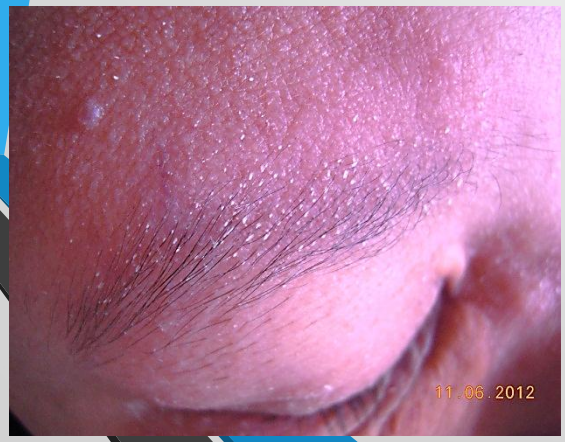


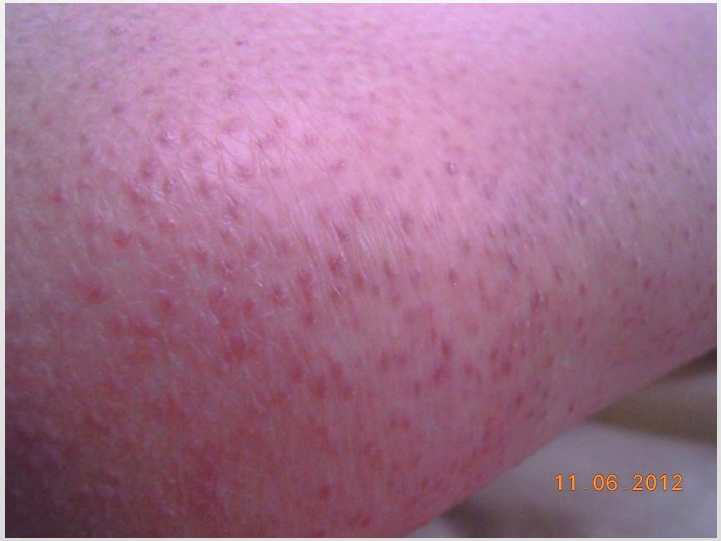


Follicular Hyperkeratosis

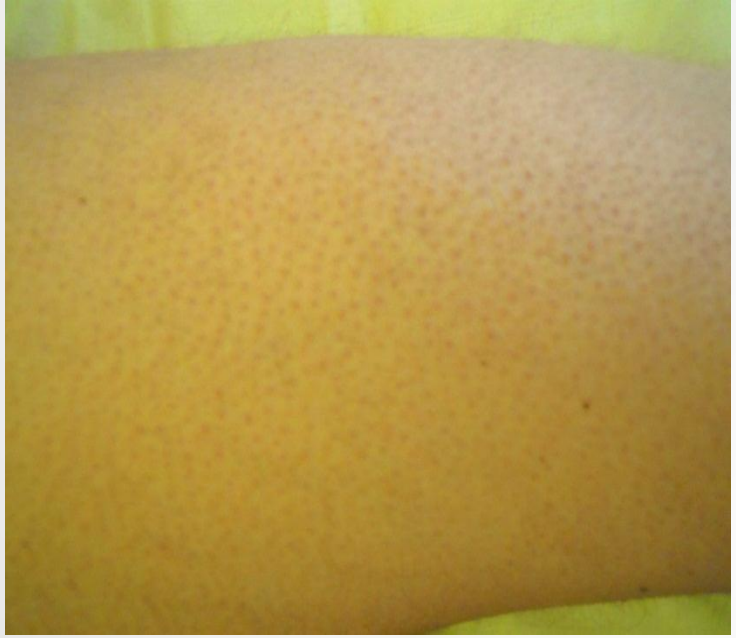
Most frequent AE (60%)
Start D7 or later
Emollient usefull
Exfoliative cream

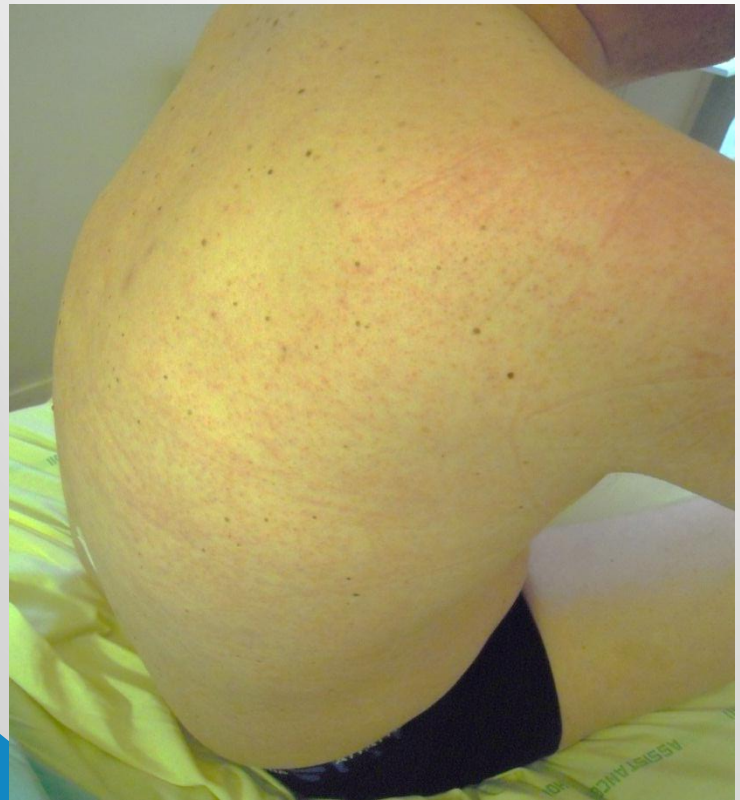






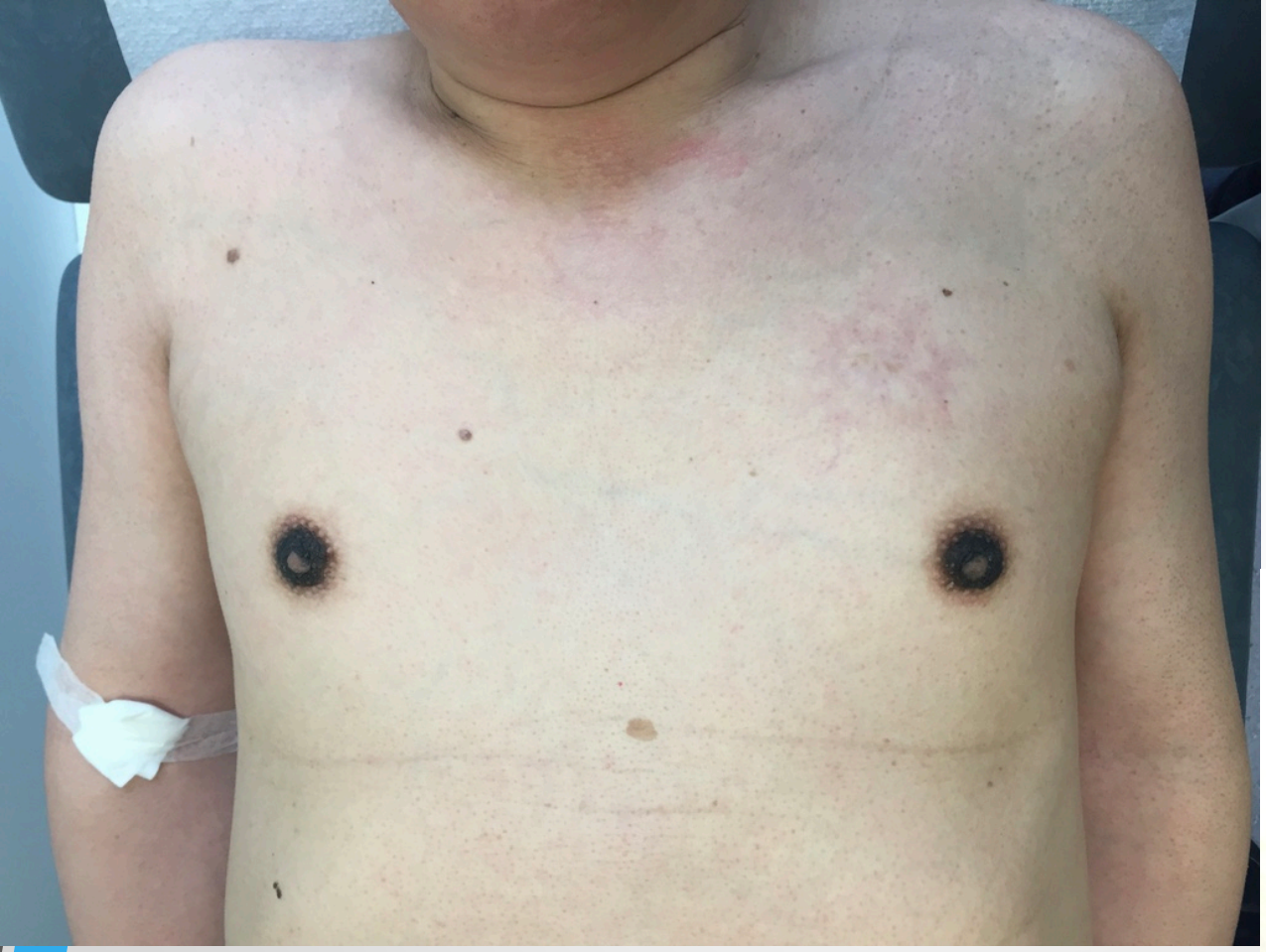
Hyperkeratotic papules





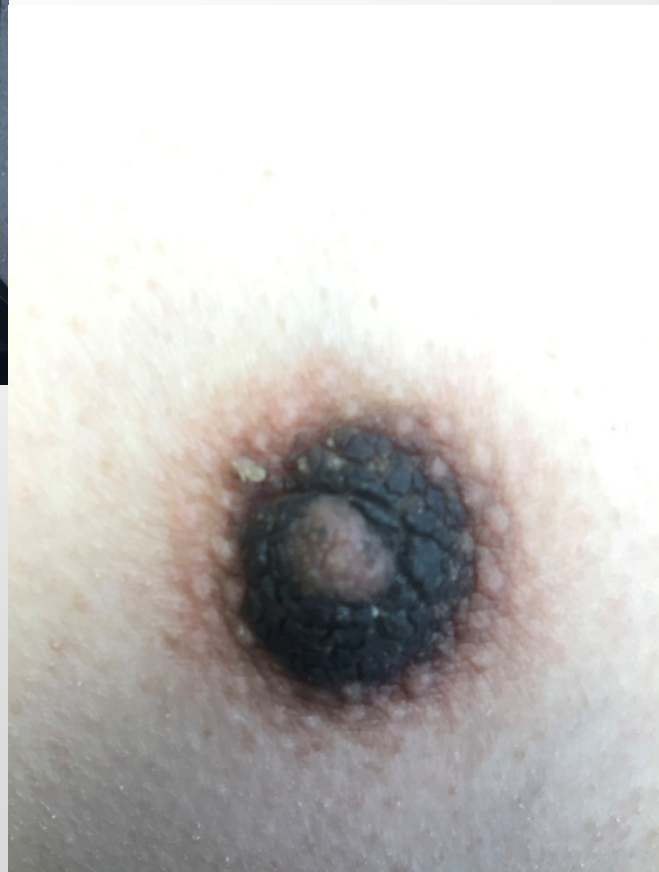
Follicular hyperkeratosis of the limbs and back

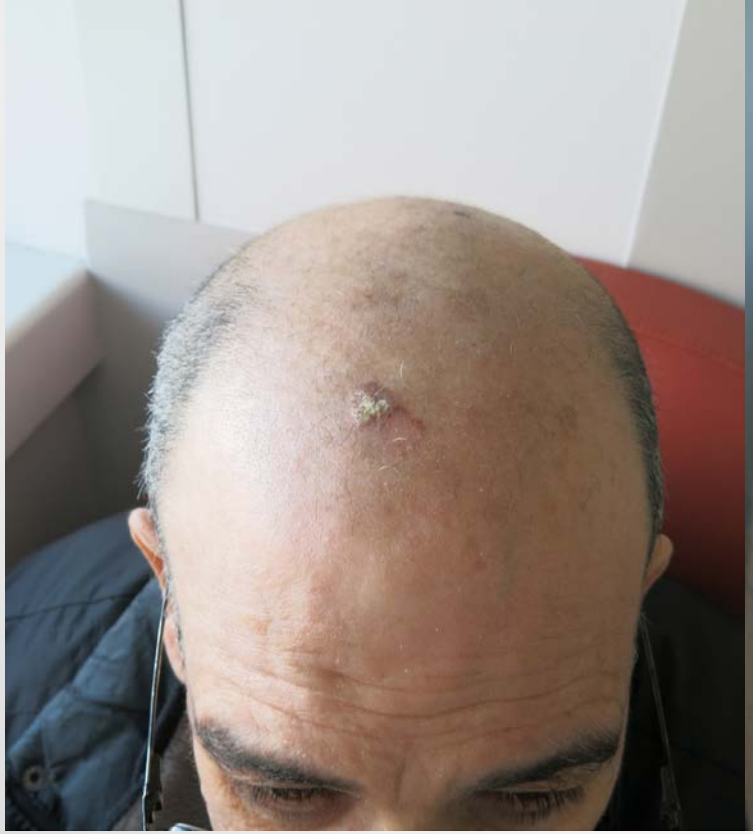
Itching
Aesthetical impairment
Moisturizing cream
Exfoliating cream
Educational program: Inform the patient

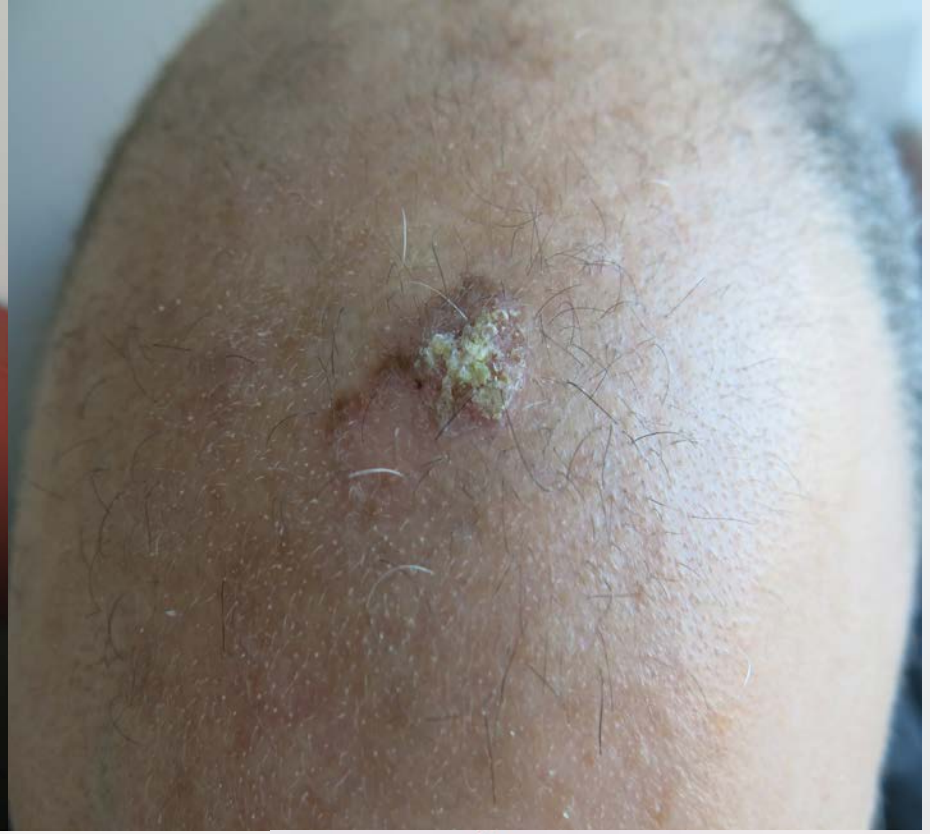


Kyperkeratosis of the nipples and areola after 3 months of vemurafenib

Martinez Garcia E et al . Clinical and experimental dermatology 2016; 41 : 148-151

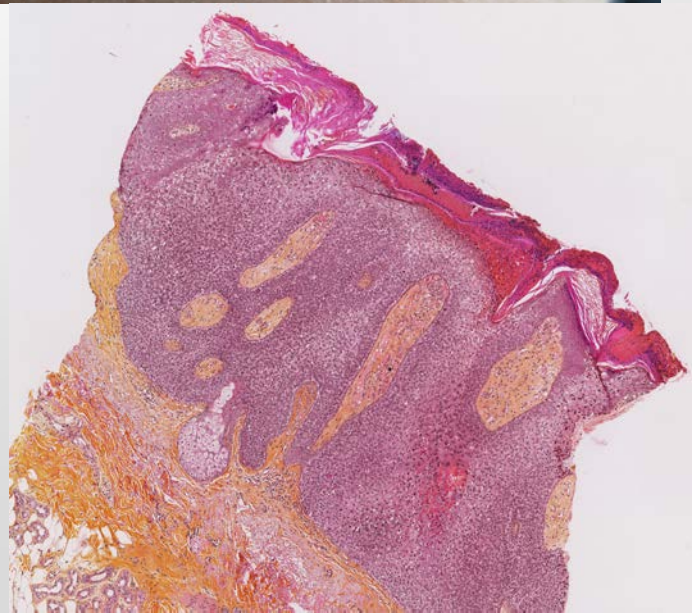


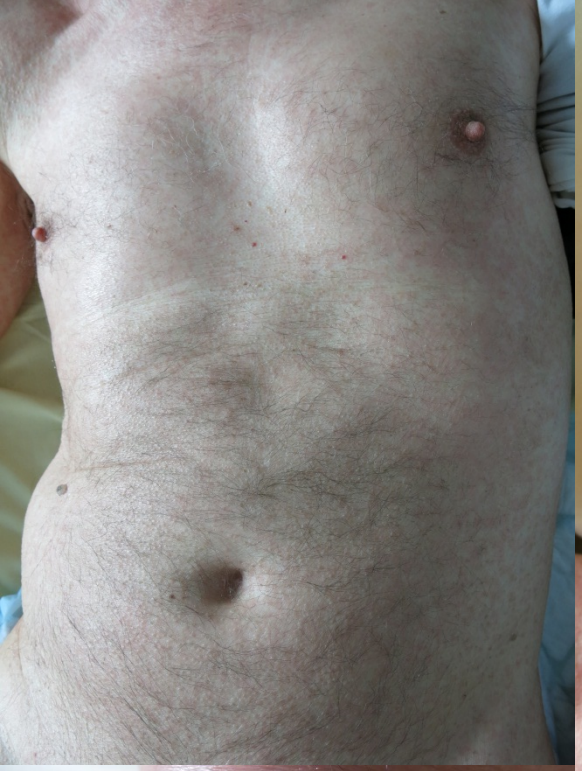


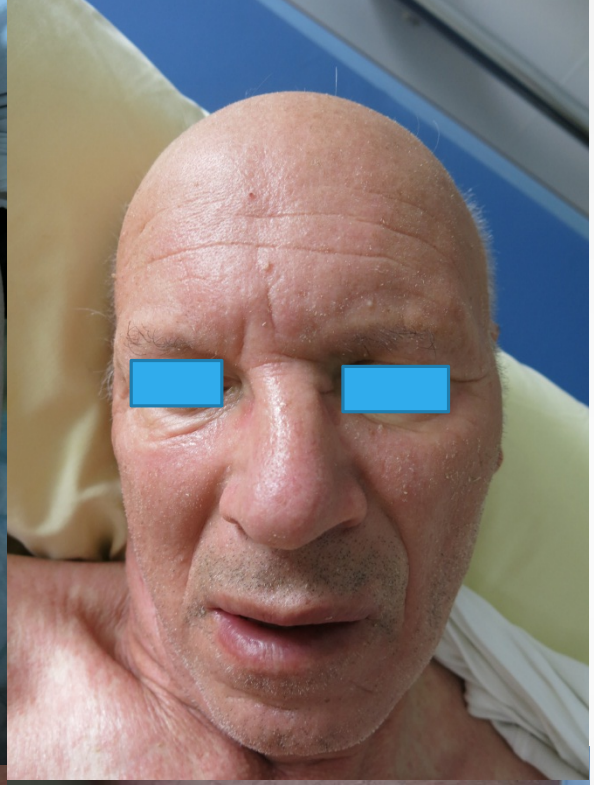


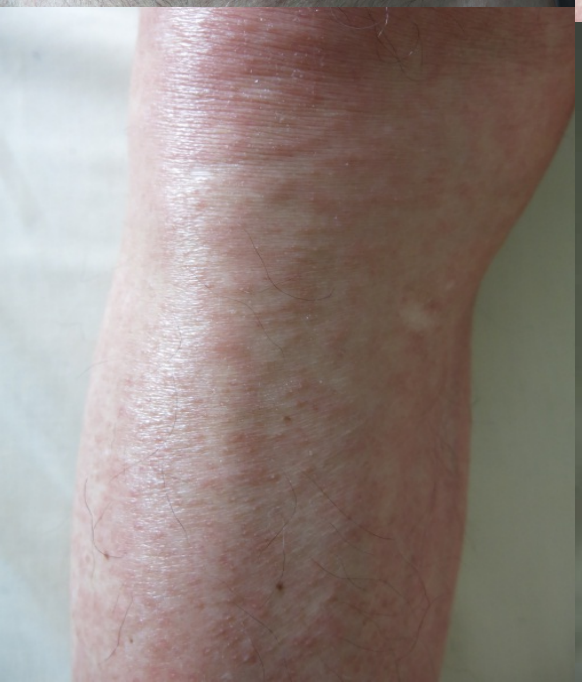
Bowen disease/ squamous cell carcinoma

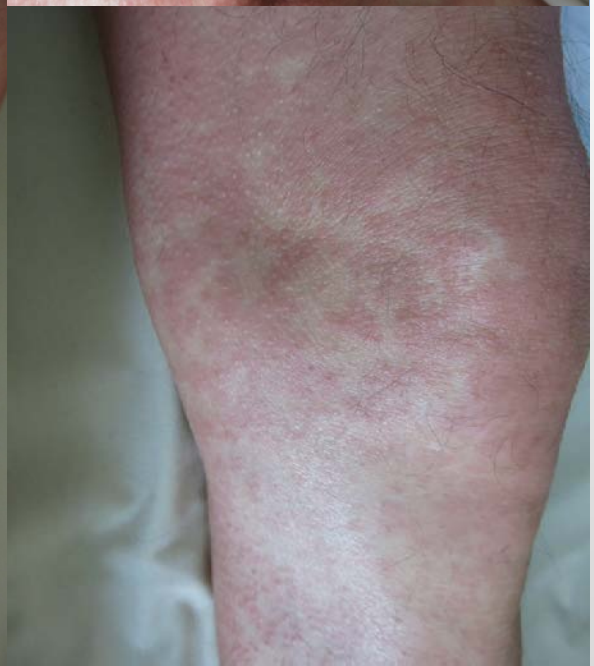
- Onset < 3 months
- Or later
- UV prevention ++
- Education











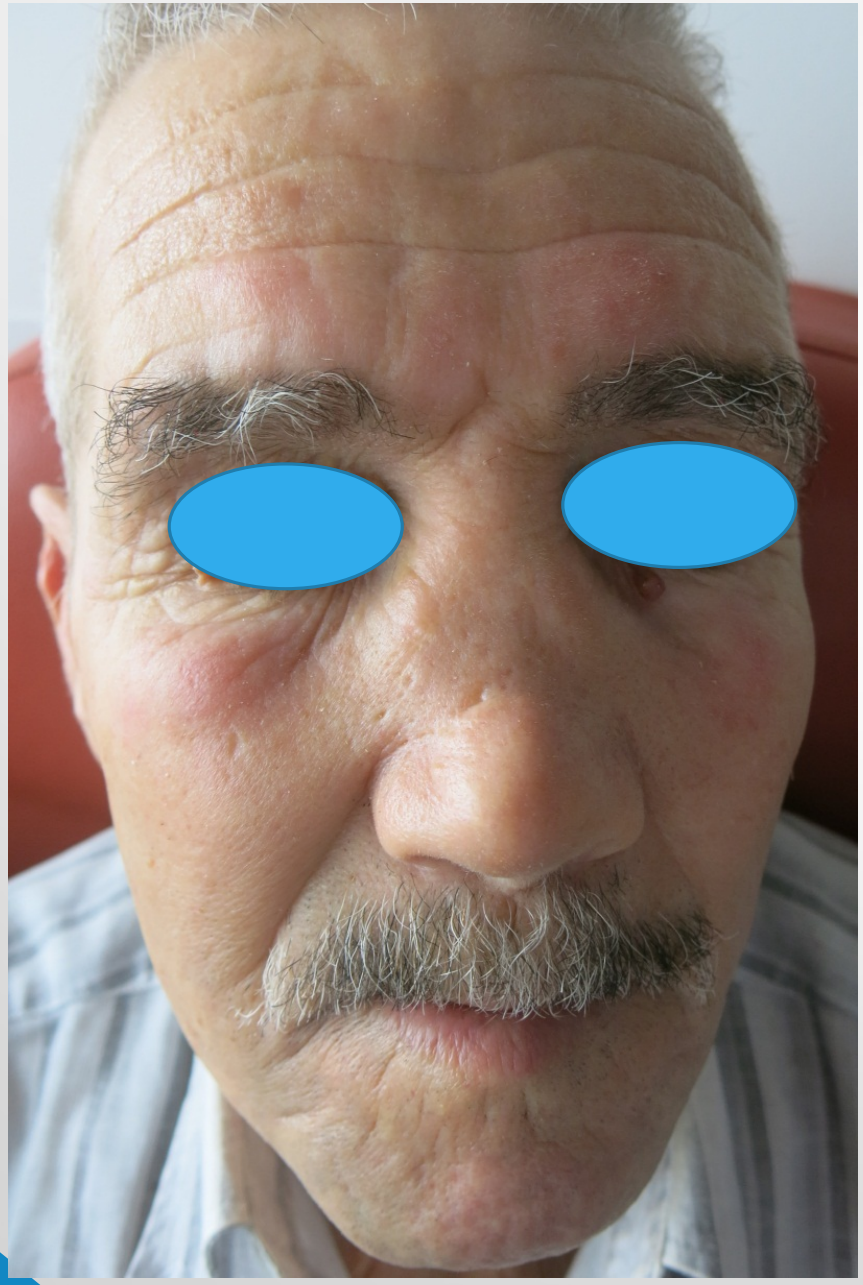
DRESS with vemurafenib

- Potential life threatening
- Need to stop drug
- Declare for PV
- Crossreact with dabrafenib

1: Wenk KS, Pichard DC, Nasabzadeh T, Jang S, Venna SS. Vemurafenib-induced DRESS. JAMA Dermatol. 2013 Oct;149(10):1242-3.

2: Gey A, Milpied B, Dutriaux C, Mateus C, Robert C, Perro G, Taieb A, Ezzedine K, Jouary T. Severe cutaneous adverse reaction associated with vemurafenib: DRESS, AGEP or overlap reaction? J Eur Acad Dermatol Venereol. 2014 Aug 29.

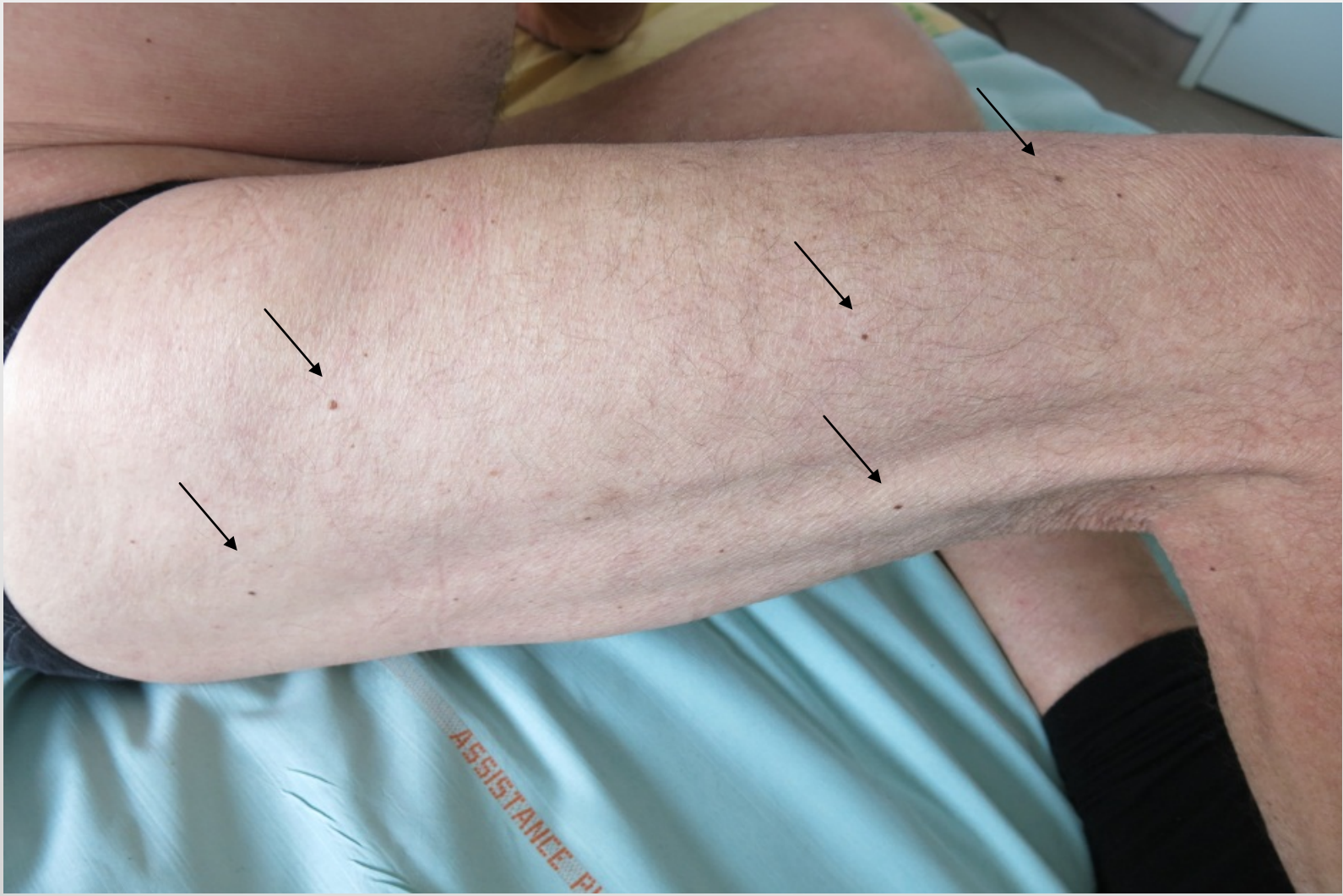
3: Munch M, Peuvrel L, Brocard A, Saint Jean M, Khammari A, Dreno B, Quereux G. Early-Onset Vemurafenib-Induced DRESS Syndrome. Dermatology. 2015 Sep 30.



Facial photosensitivity with Combi-therapy (vemurafenib and cobimetinib)

- Prevention
- Explanation
- Education
- Sun protection

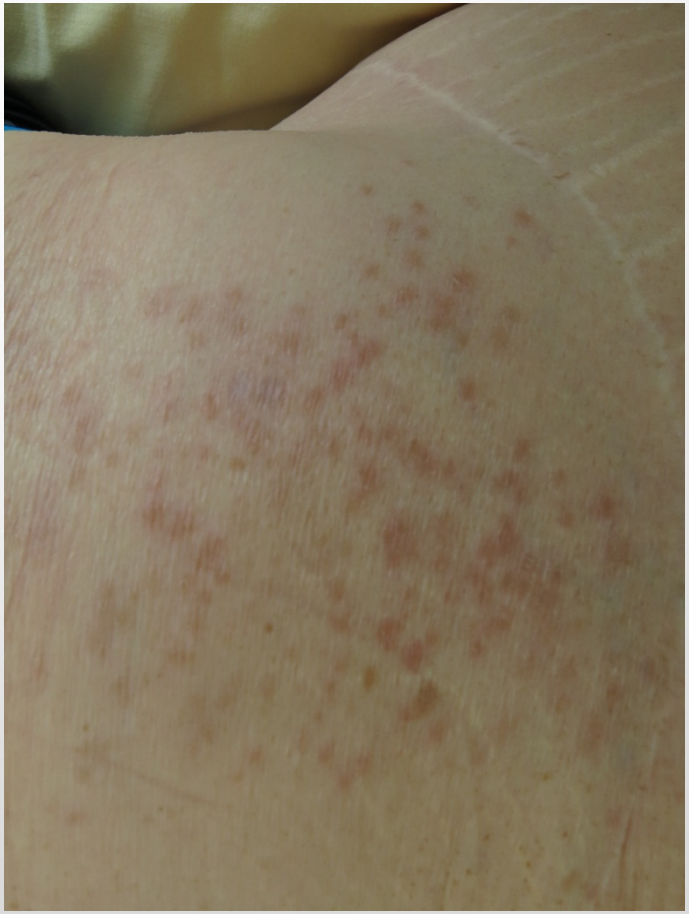
Eruptive melanocytic Naevi with vemurafenib
Risk for primary melanoma: follow-up+++



Dalle. S et al J AMA dermatol 2013; 149:488-490

Sarcoidosis granuloma induced by vemurafenib

Lheure C et al. Dermatology 2015; 231:378-84



My practice guidelines

- Avoid sun exposure with protective sun cream with SPF 50 and protective dressing
- Educate patient to auto-screening of skin lesions to report to practitioner/dermatologist
- Talk with patients about frequency and severity of AEs
- Check skin with regular evaluation and referral once a month for 3 months then each 3 months
- Include patients in observational study like ACséVému (Unicancer) for best detection and screening of AEs with MTT

Conclusion

- Skin issues in ECD
  - Diagnosis: XLL++
  - BRAF mutational status: easy, safe and usefull from skin
- Skin MTT toxicities
  - Increasing with emerging therapies (signalling pathways)
  - Mostly manageable, sometime stop MTT
  - Need to be checked regularly and evaluated
  - Learn about physiopathology of the disease whatever mutational status of BRAF
  - Need for gathering cohorts of ECD patients for skin follow-up under MTT

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- Patients…