Systemic Xanthogranuloma or Erdheim-Chester Disease: Time to Revisit the Nomenclature?

Vyshnavi Rallapalle BS[1], Tanvi Bhadkamkar BS[1]; Brinda Shukla[2]; Jithma P. Abeykoon MD[3], Mitali Sen MD[4], Ronald S. Go MD[3], Craig Elmets MD[5], Rhodemarie Maron DO[6] , Jonathan McConathy MD PhD[7], Aishwarya Ravindran MD[8] , Gaurav Goyal MD[9]

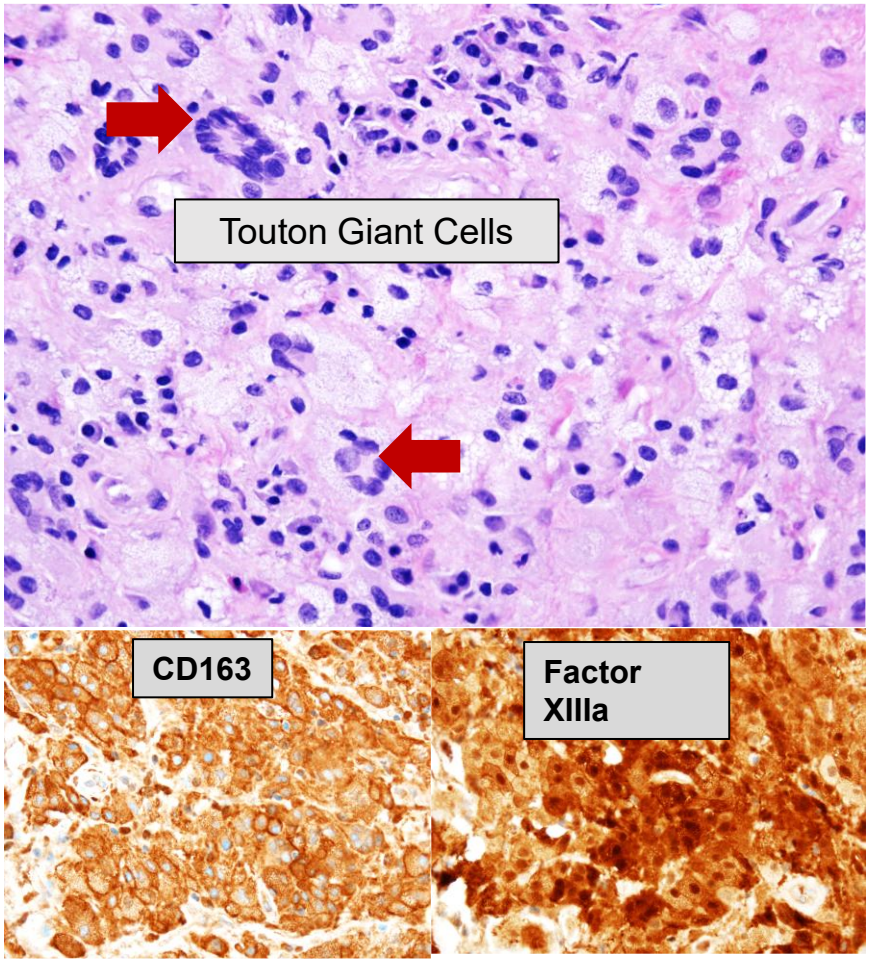
[1]Heersink School of Medicine, University of Alabama at Birmingham, AL, United States
[2] Department of Cancer Biology, College of Arts & Sciences, University of Alabama at Birmingham, AL, United States
[3]Division of Hematology, Mayo Clinic, Rochester, MN, United States
[4]Division of Rheumatology, University of Alabama at Birmingham, AL, United States
[5]Department of Dermatology, University of Alabama at Birmingham, AL, United States
[6]Department of Neurology, University of Alabama at Birmingham, AL, United States
[7]Department of Radiology, University of Alabama at Birmingham, AL, United States
[8]Division of Hematopathology, University of Alabama at Birmingham, AL, United States
[9]Division of Hematology-Medical Oncology, University of Alabama at Birmingham, AL, United States

Disclosures

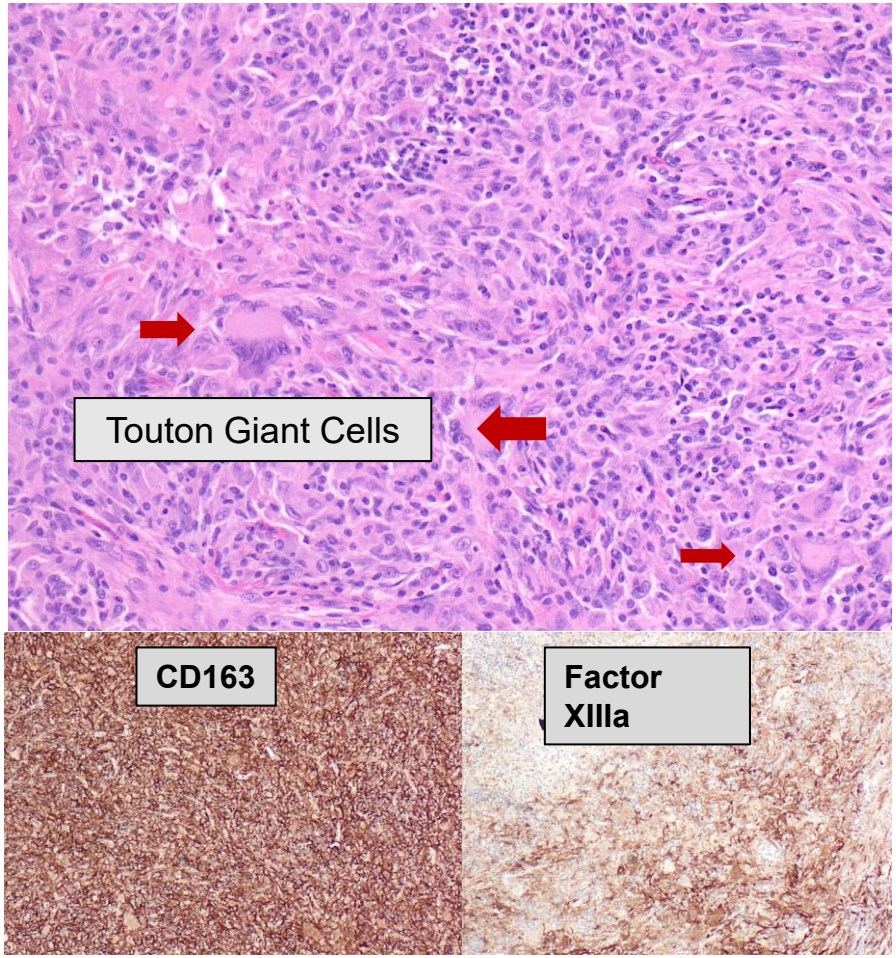
- No financial disclosures
- No conflicts of interest

Is There a Morphological Distinction between ECD and Xanthogranuloma?

Erdheim Chester Disease (ECD)



Xanthogranuloma Family (XG)



ECD: First Description

Über Lipoidgranulomatose[1].

Von

Dr. William Chester, New-York.

Mit 9 Abbildungen im Text.

(Eingegangen am 29. Mai 1930.)

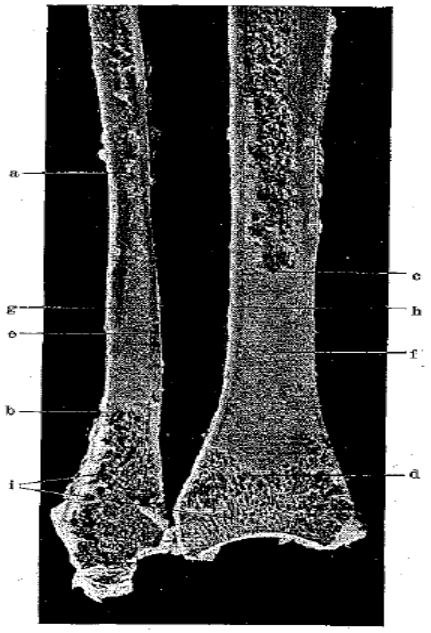
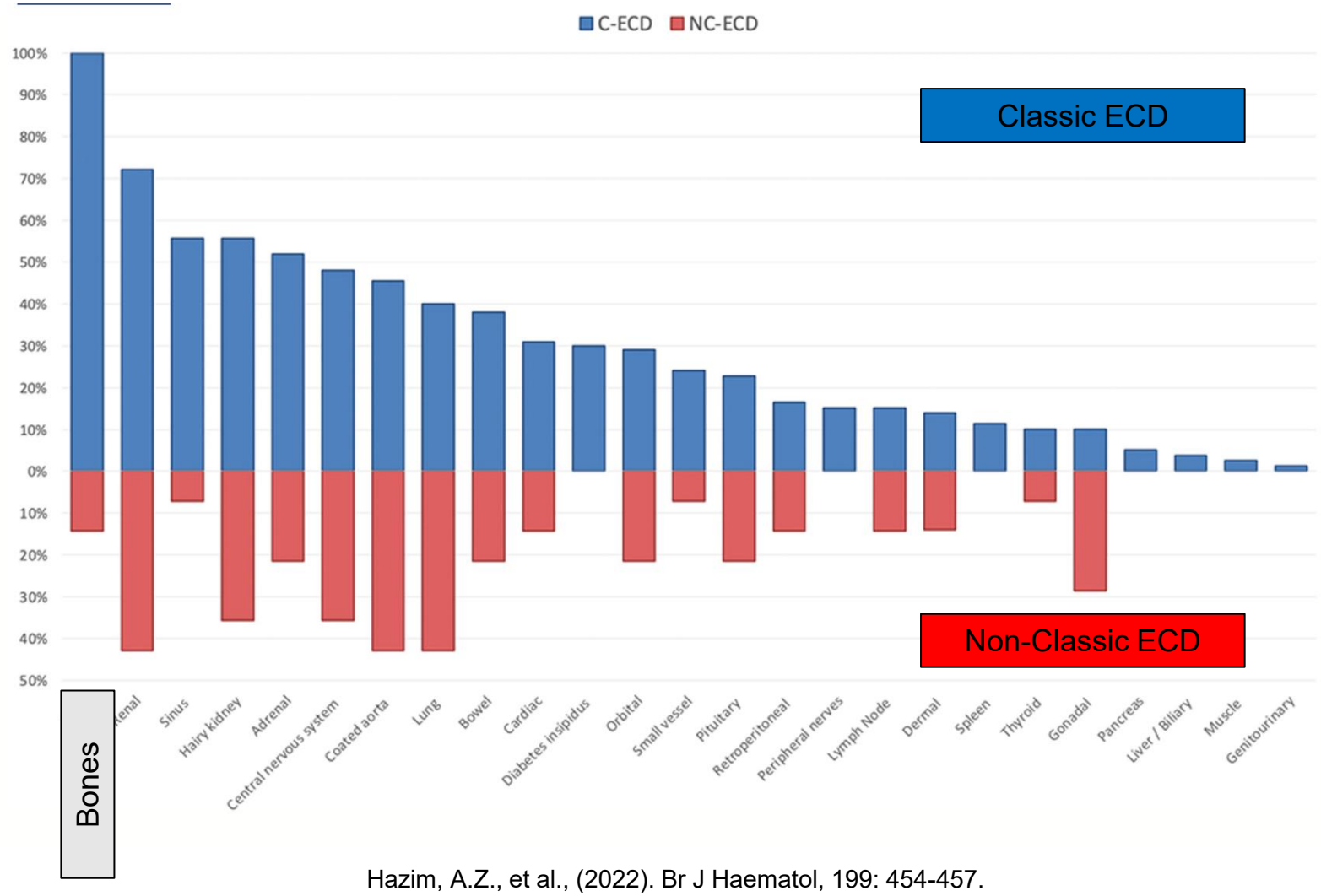


Abb. 1. Osteosklerotische Lipoidgranulomherde der Tibia und Fibula. In der rechten Fibula A und der rechten Tibia B je ein großer osteoplastischer Lipoidgranulomherd a—b, c—d, deren dichtes Knochengewebe e, f, sich gegen die dicke Knochenrinde g h deutlich abhebt. Normale Spongiosa.

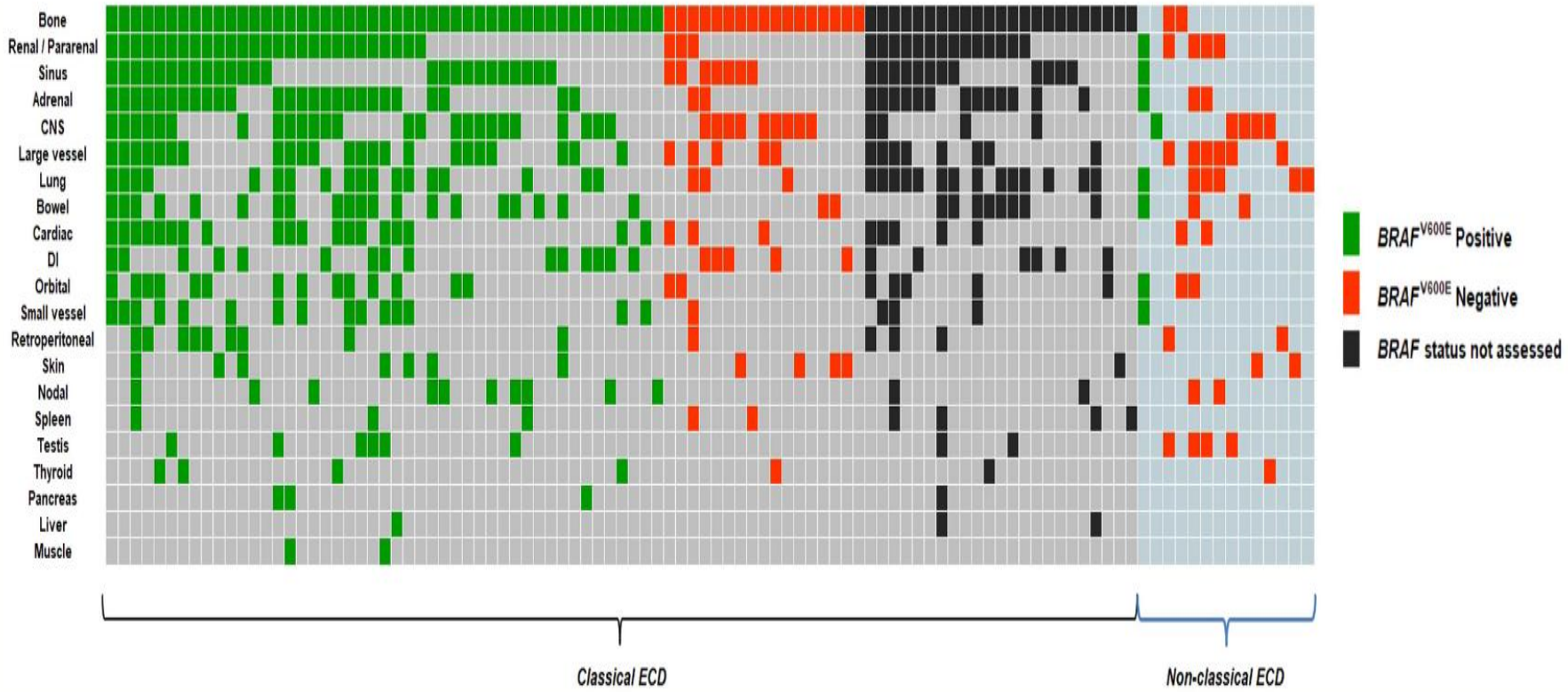
Chester W. Virchows Arch Pathol Anat 1930;279:41

Classical vs. Non-classical ECD



Hazim, A.Z., et al., (2022). Br J Haematol, 199: 454-457.

Classical vs. Non-classical ECD



Hazim, A.Z., et al., (2022). Br J Haematol, 199: 454-457.

Histiocyte Society Classification (2016)

L-group

- Langerhans cell histiocytosis (LCH)
- Erdheim-Chester disease (ECD)
- Classical ECD
- Nonclassical ECD
- Mixed LCH/ECD
- Indeterminate cell histiocytosis
- ALK-positive histiocytosis

C group

- Cutaneous (skin) non-LCH
  - Xanthogranuloma family (JXG, AXG)
  - Non-xanthogranuloma family (Rosai-Dorfman, Necrobiotic xanthogranuloma)
- Cutaneous non-LCH with systemic component
  - XG family- XD
  - Non-XG family - MRH

Emile JF et al, Blood. 2016 Jun 2;127(22):2672-81

World Health Organization, 5th ed. (2022)

Histiocytic neoplasms

- Juvenile xanthogranuloma (JXG)
- Erdheim-Chester disease
- Rosai-Dorfman disease
- ALK-positive histiocytosis
- Histiocytic sarcoma

Khoury JD et al. Leukemia (2022). https://doi.org/10.1038/s41375-022-01613-1

Methods

- Comprehensive review of published cases of adult xanthogranuloma (AXG) (age ≥18y) with extracutaneous involvement from 2013-2024 through PubMed and Embase
- Search terms included “adult AND xanthogranuloma” with additional searches including the terms “systemic,” “extracutaneous,” “multiple,” “multifocal,” “multicentric,” and “visceral”

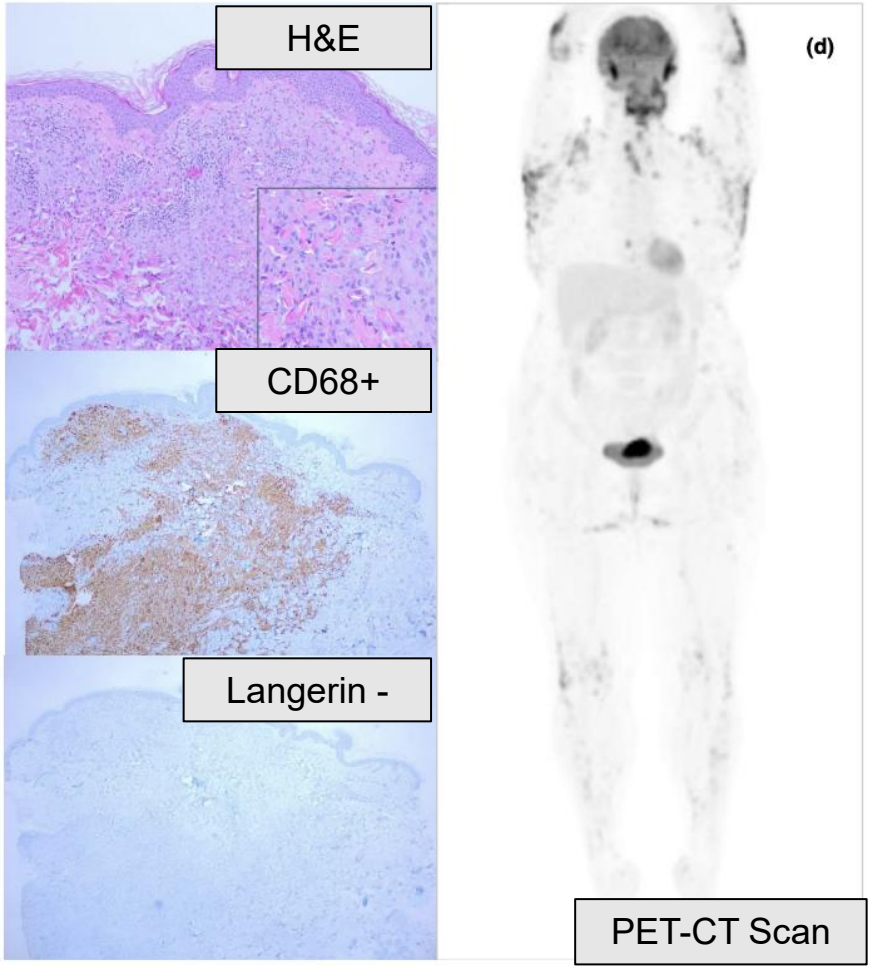
THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

HEERSINK SCHOOL OF MEDICINE

Cases from the Literature

1) AXG w/ upper airway involvement

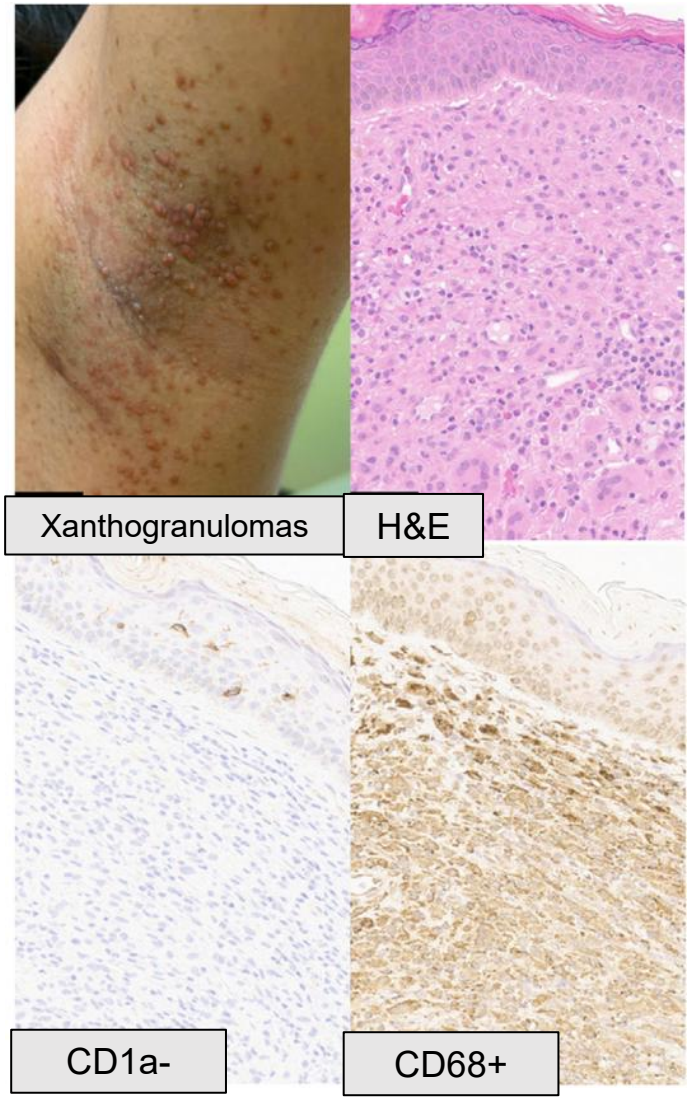
- 57 y/o female
- Skin lesions involving axilla, trunk, perioral, and periocular areas
- Oropharynx and glottic involvement
- BRAFV600E neg
- Full body PET/CT shown
- Spontaneous regression of all lesions in 24 months



Sampedro-Ruiz, et al., (2021). Int J Dermatol, 60: e317-e319.

2) AXG w/ brain/pituitary involvement

- 22 y/o female
- Cutaneous lesions: face, axilla, groin
- Extracutaneous sites: brain and pituitary
- PET-CT scan performed
- GAB2-BRAF fusion
- Partial response to prednisone treatment



Wu B, et al. Cutan Pathol. 2022;49(8):727-730

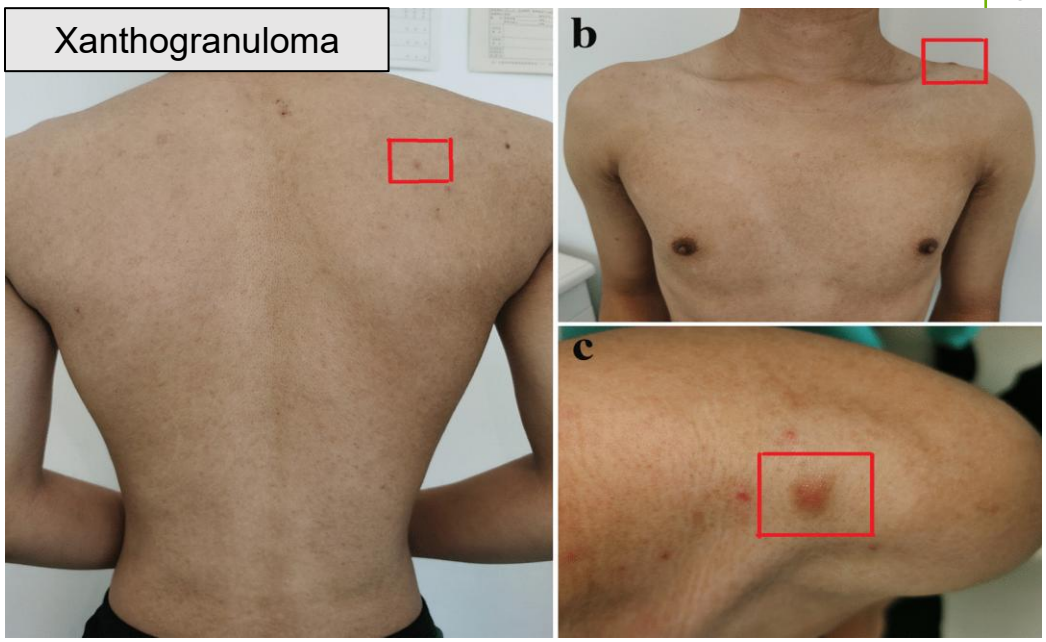
3) AXG w/ lung & scleral involvement

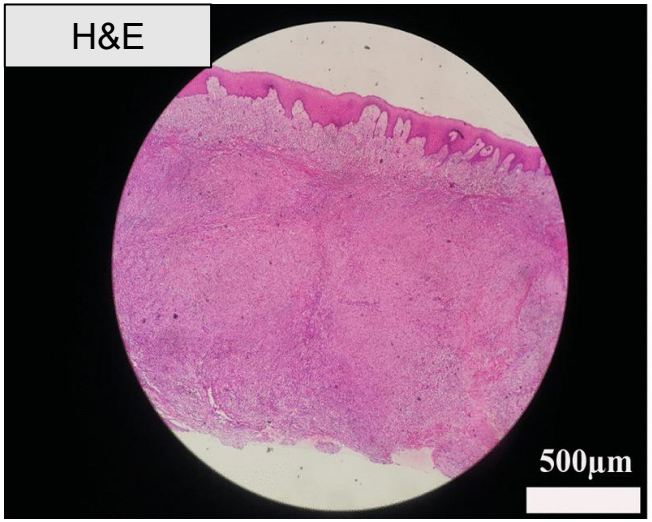
- 60 y/o female with numerous skin lesions and lung and scleral involvement
- UBR2-BRAF fusion
- Treatment and outcome not specified

Zanwar, S., et al., (2022). Blood cancer journal,12(6), 97. (Reference Table 1- Pt #: MC-6)

4) AXG w/ gingival involvement

- 21 y/o male
- Cutaneous lesion on shoulder
- Extracutaneous site: mandibular gingiva
- No baseline imaging or mutational testing
- Patient declined treatment



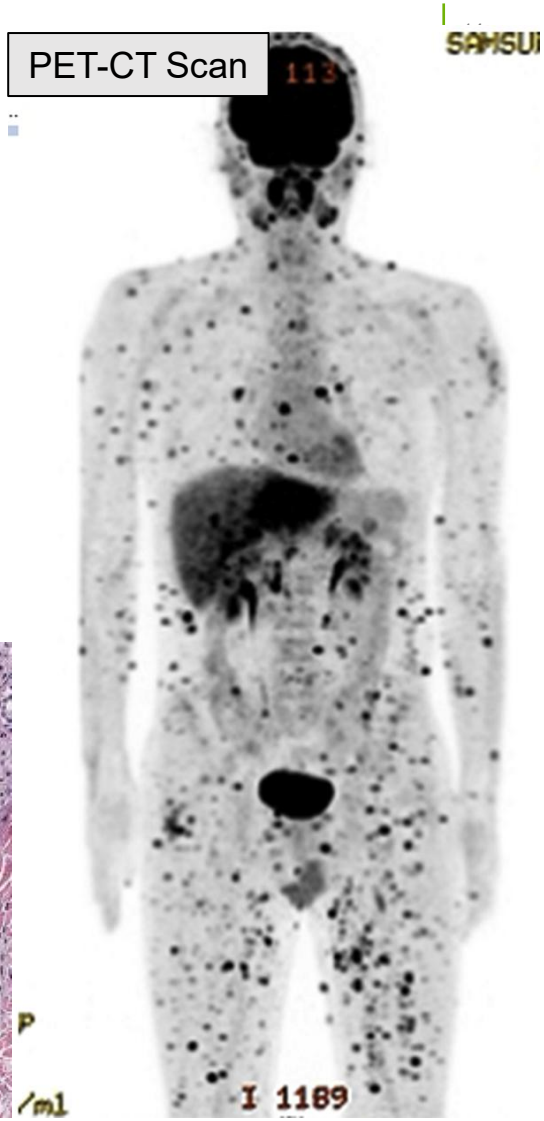


Chen, L., et al., (2022). BMC oral health, 22(1), 618.

5) AXG w/ multisystem involvement

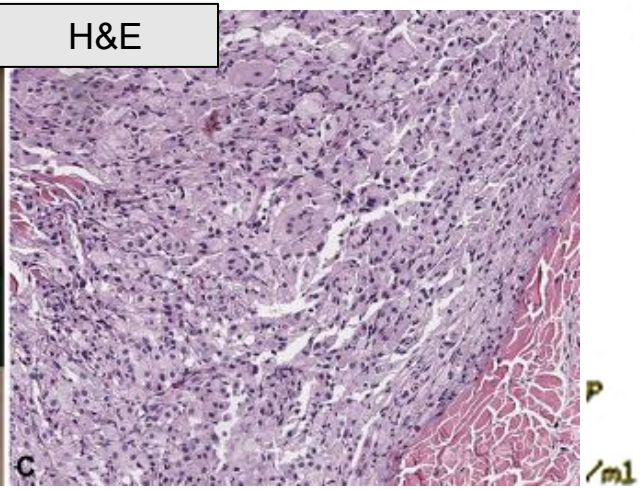
- 31 y/o male
- Cutaneous lesions: face, trunk, legs
- Extracutaneous lesions: liver, pancreas, lungs, bones
- PET-CT performed
- No mutational testing performed
- Observation of lesions w/ no outcome specified

PET-CT Scan



Xanthogranulomas

H&E

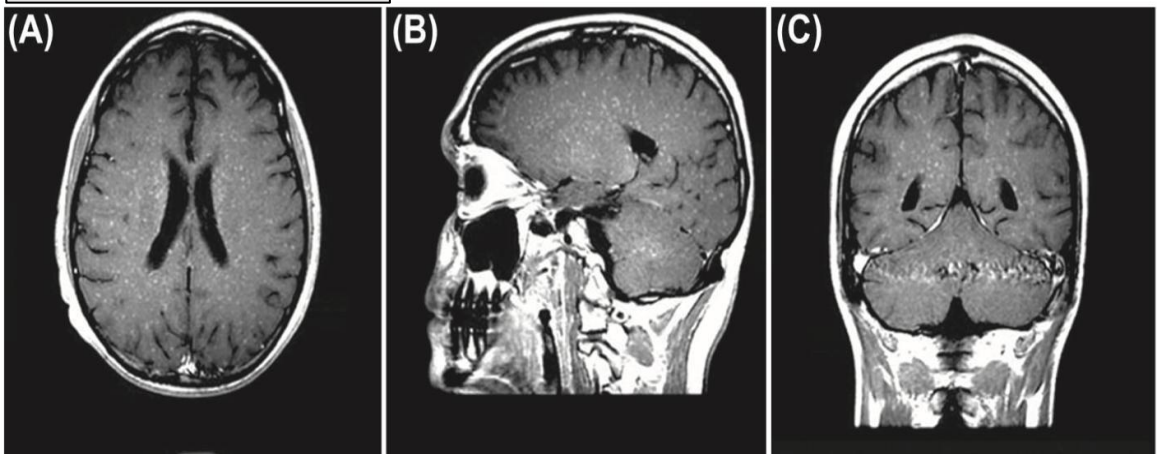


Yoon, D., et al., (2019). JAAD case reports, 5(12), 1097–1100.

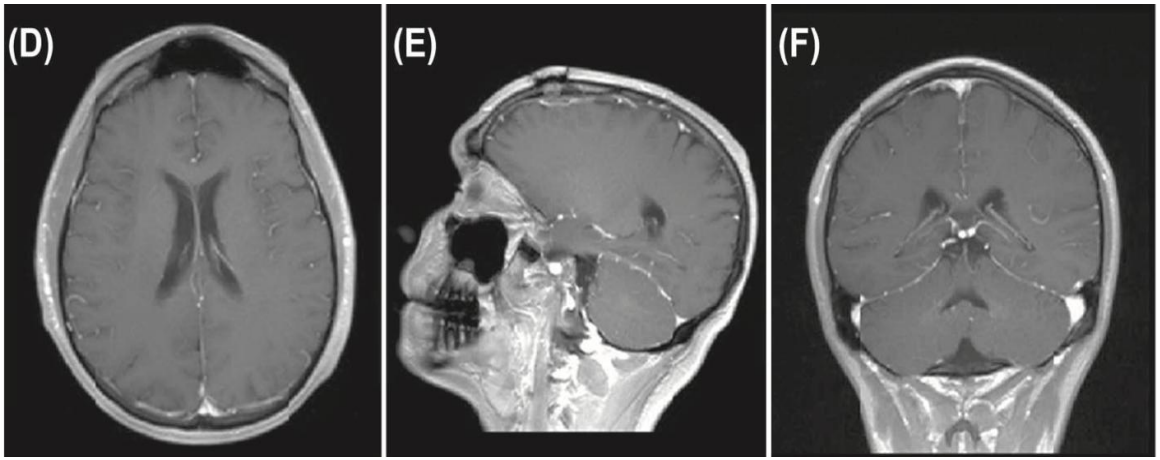
6) AXG w/ brain involvement

- 23 y/o male
- One skin lesion- resolved spontaneously
- Multiple intracranial xanthogranulomas
- No PET-CT scan performed
- No mutational testing performed
- Intracranial lesions resolved w/ steroids and chemotherapy

Pre-Treatment MRI



Post-Treatment MRI



Lee A. Tan, et al., (2014). British Journal of Neurosurgery, 28:6, 817-818

Summary

Case	PMID	Age/Gender	Skin lesion location(s)	Other organs involved	Knee bone osteosclerosis	Baseline full body imaging	Mutational testing	Treatment and outcome
1	33560521	57/F	Axilla, trunk, perioral, periocular	Oropharynx, glottis	-	PET-CT	BRAF V600E neg	Spontaneous regression
2	35332933	22/F	Face, oral mucosa, axilla, groin	Brain, pituitary	-	PET-CT	GAB2-BRAF	Prednisone-partial response
3	35764604	60/F	Not specified	Lung, sclera	-	None	UBR2-BRAF	Not specified
4	36529720	21/M	Shoulder	Gingiva	-	None	None	None-declined treatment
5	31828195	31/M	Face, trunk, legs	Liver, pancreas, lungs, muscles, bones	-	PET-CT	None	Observation-not specified
6	24827069	23/M	Not specified	Brain	-	None	None	Steroids/ Chemotherapy-complete resolution

Conclusions

- Non-classical ECD and systemic involvement of XG in adults are morphologically indistinguishable from each other.
- Half of the cases did not undergo baseline PET-CT scan or mutational testing.
- Systematic evaluation may be needed for adults with XG lesions.
- There is a need to better define non-classic ECD to differentiate it from systemic AXG.

Acknowledgements

Patients and Families

Mentors & Collaborators

UAB:
Dr. Gaurav Goyal
Dr. Aishwarya Ravindran
Dr. Mitali Sen
Dr. Craig Elmets
Dr. Rhodemarie Maron
Dr. Jonathan McConathy

Research Team (UAB)
Caroline Cannon
Lindsey Hageman
Brinda Shukla
Tanvi Bhadkamkar
David Pottinger
Chinonso Udensi

Mayo Clinic:
Dr. Ronald Go
Dr. Jithma Abeykoon

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM.

HEERSINK SCHOOL OF MEDICINE

Questions?