

***WHO* has an update on the Histiocytoses?...Check your *Blood*: A brief update on the pathogenesis and histopathology of histiocytic neoplasms**

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Society for Hematopathology
Companion Meeting USCAP 2017

MOVING  **INFORMATION**

106TH
ANNUAL MEETING

 **USCAP**
Creating a Better Pathologist

Revised classification of histiocytoses and neoplasms of the macrophage-dendritic cell lineages

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A **L Group** **

- LCH
- ICH
- ECD
- Mixed LCH/ECD

vi

vii

Fusions: *BRAF*, *ALK*, *NTRK1*
*PIK3CA**

* A proportion of *PIK3CA* mutant patients have concomitant *BRAFV600E* mutations.

B **C Group**

- Cutaneous non-LCH
- XG family: JXG, AXG, SRH, BCH, GEH, PNH
- Non-XG family: cutaneous RDD, NXG, other NOS
- Cutaneous non-LCH with a major systemic component

C **R Group**

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

D **M Group** **

- Primary Malignant Histiocytoses
- Secondary Malignant Histiocytoses (following or associated with another hematologic neoplasia)
- Subtypes: *Histiocytic*, *Interdigitating*, *Langerhans*, *Indeterminate Cell*

E **H Group**

- Primary HLH: Monogenic inherited conditions leading to HLH
- Secondary HLH (non-Mendelian HLH)
- HLH of unknown/uncertain origin

Revised classification of histiocytoses and neoplasms of the macrophage-dendritic cell lineages

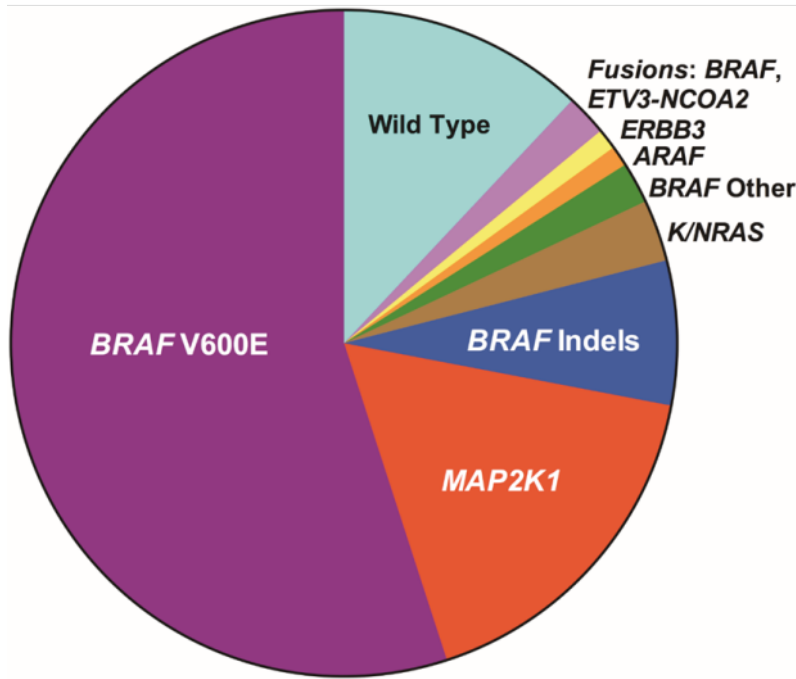
A

L Group

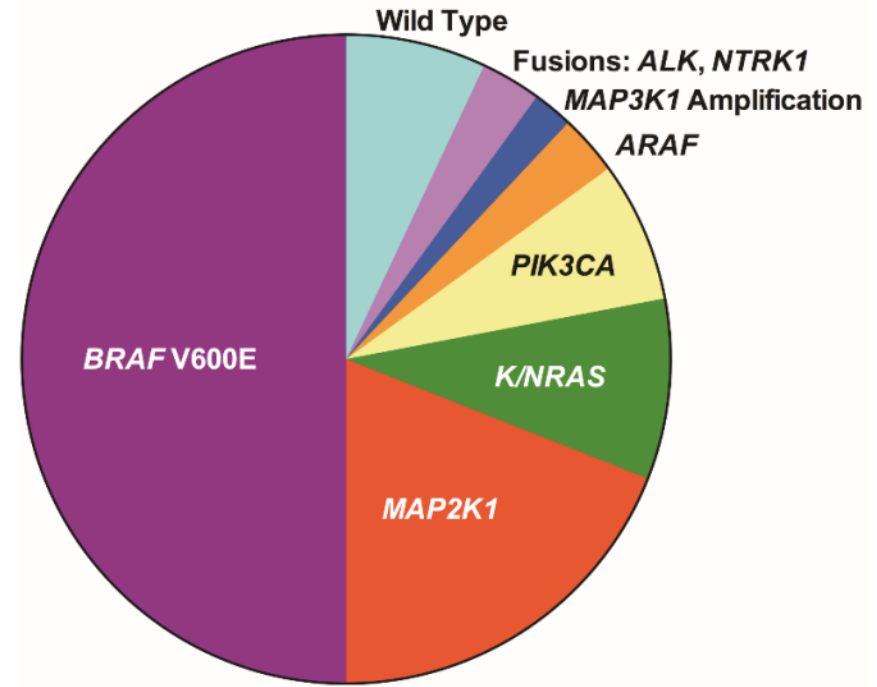
- LCH
- ICH
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Image courtesy of : Benjamin H. Durham, M.D.,
Genomic Pathology Research Fellow in Molecular Oncology
Department of Pathology Memorial Sloan Kettering Cancer Center

Langerhans cell histiocytosis (LCH)



Erdheim-Chester Disease (ECD)



Badalian-Very, et al. *Blood* 2010
Kansal, et al. *Genes Chrom Cancer* 2013
Brown NA, et al. *Blood* 2014
Chakraborty, et al. *Blood* 2014
Nelson, et al. *Genes Chrom Cancer* 2015

Chakraborty et al. *Blood* 2016
Lee et al. *JCI Insight* 2017

Haroche, et al. *Blood* 2012
Diamond, et al. *Blood* 2013
Go, et al. *Histopathology* 2014
Emile, Diamond, et al. *Blood* 2014
O'Malley, et al. *Ann Diagn Pathol* 2015
Kordes, et al. *Leukemia* 2015

Brown RA, et al. *Blood* 2015
Diamond, Durham, Haroche, et al. *Cancer Discovery* 2016
Durham, et al. *Curr Opin Hematol.* 2016
Shanmugam, et al. *Head Neck Pathol.* 2016
Lee, et al. *JCI Insight* 2017

“L” group

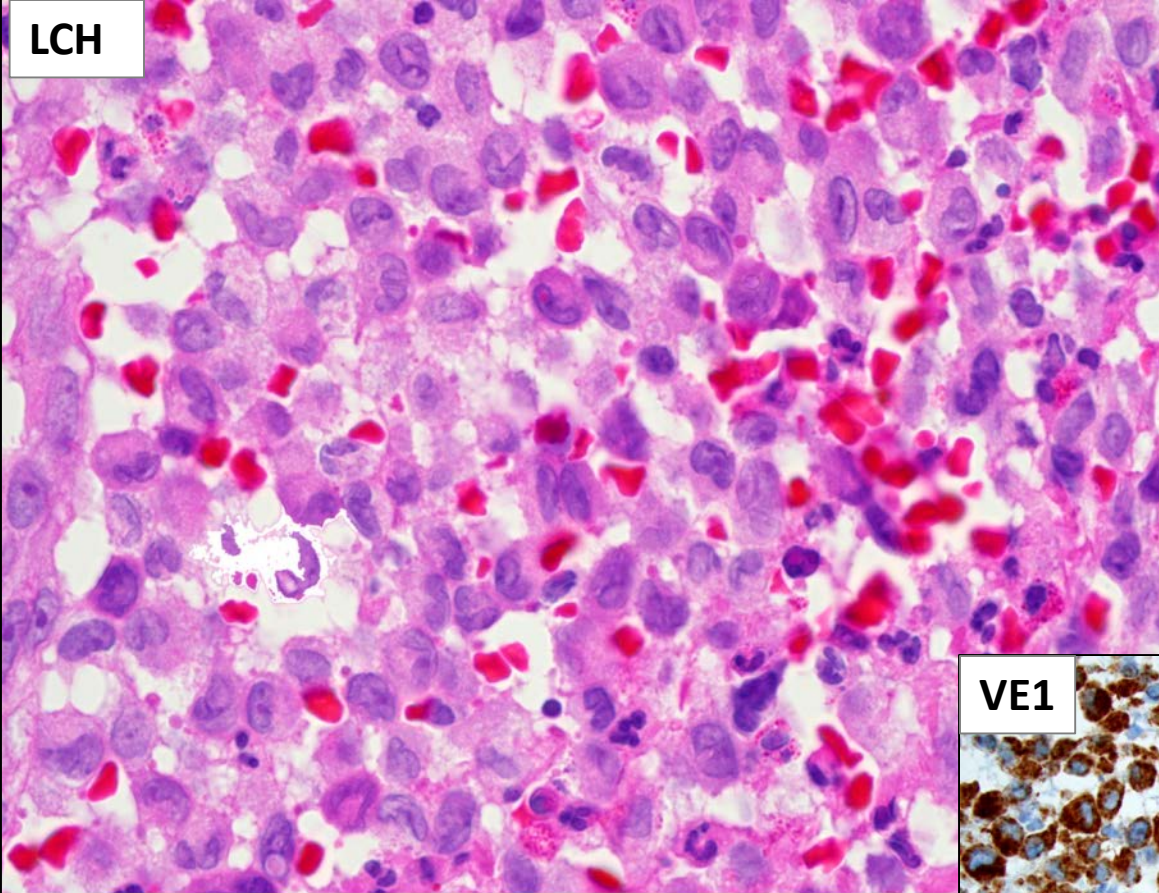
Table 1. Histiocytoses of the L group

| 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

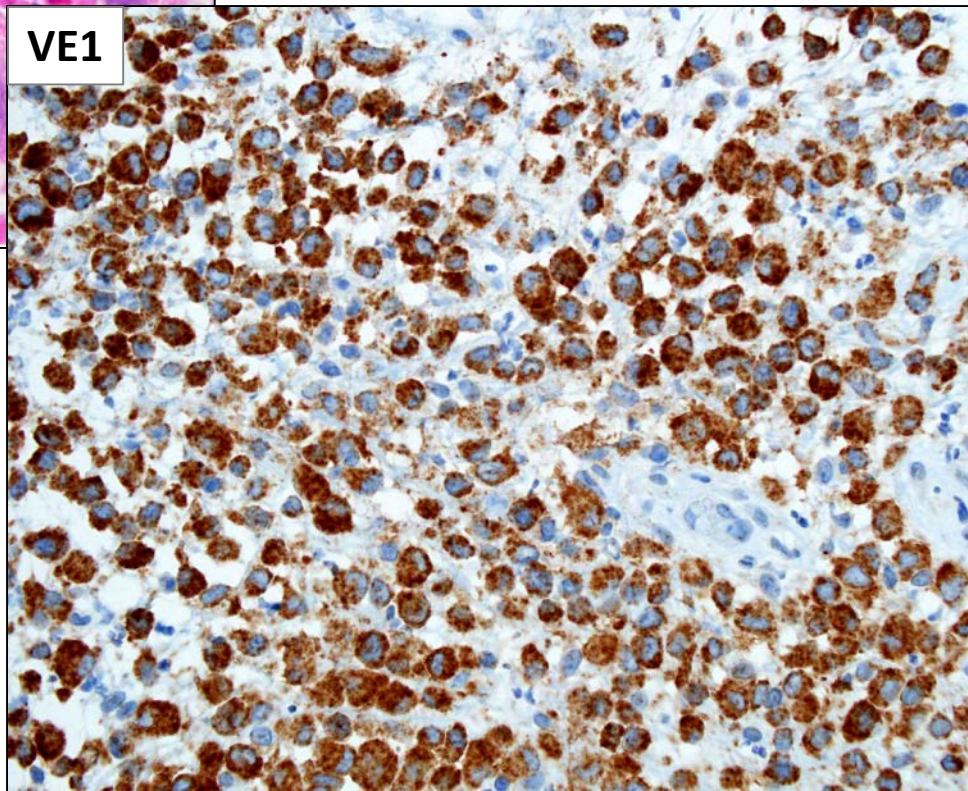
ECD, Erdheim-Chester disease; ICH, indeterminate cell histiocytosis; LCH, Langerhans cell histiocytosis; MS, multiple system; RO, risk organ; SS, single system.

LCH



38 yo F with
both skin LCH
and ECD

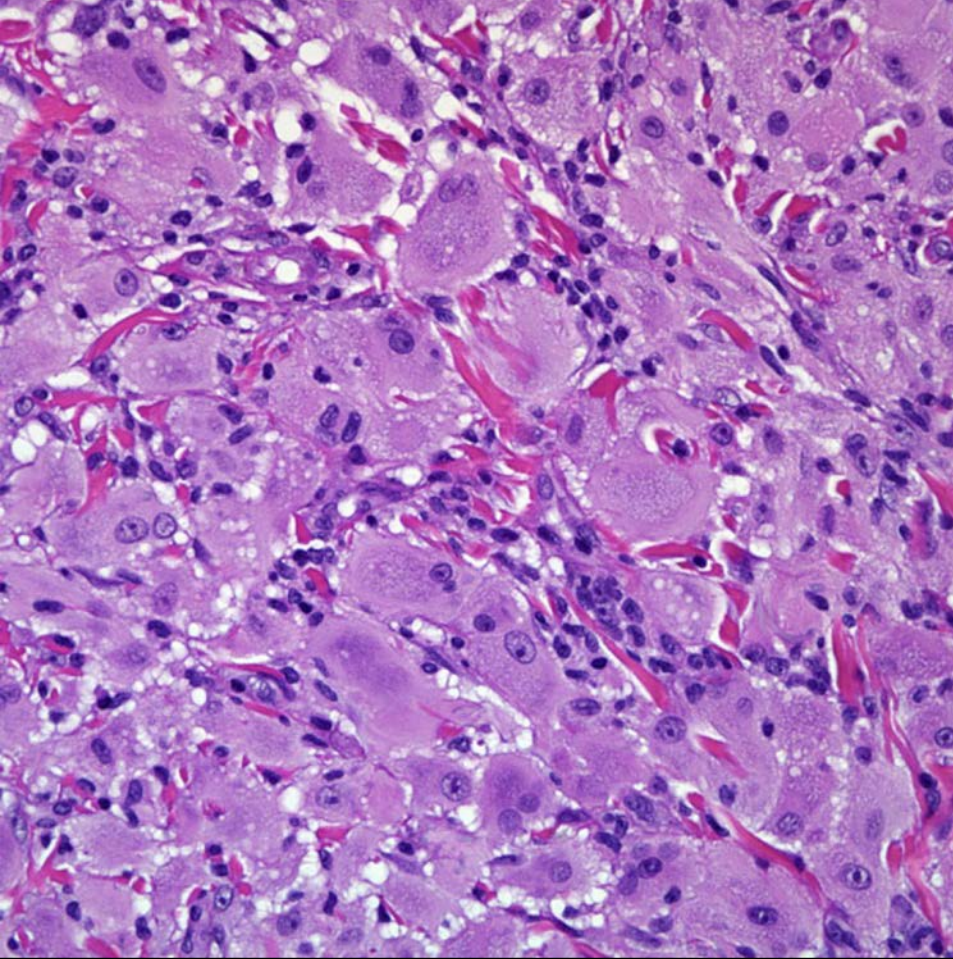
VE1



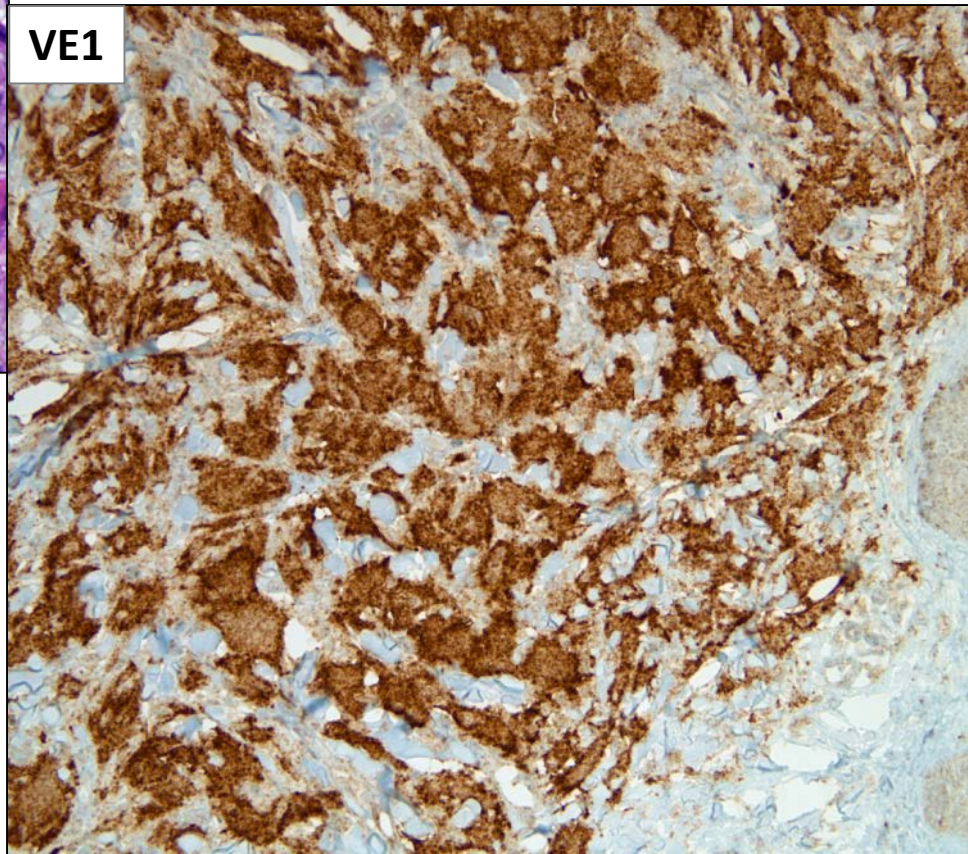
Original skin biopsy
of LCH, later shown
to also be VE1+

Johnson et al. J Cutan Pathol. 2015.
Mar;43(3):270-5.

38 yo F with both skin LCH and ECD



VE1

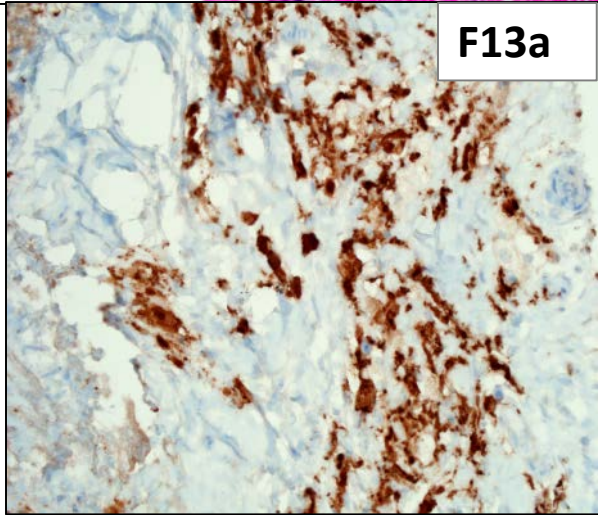
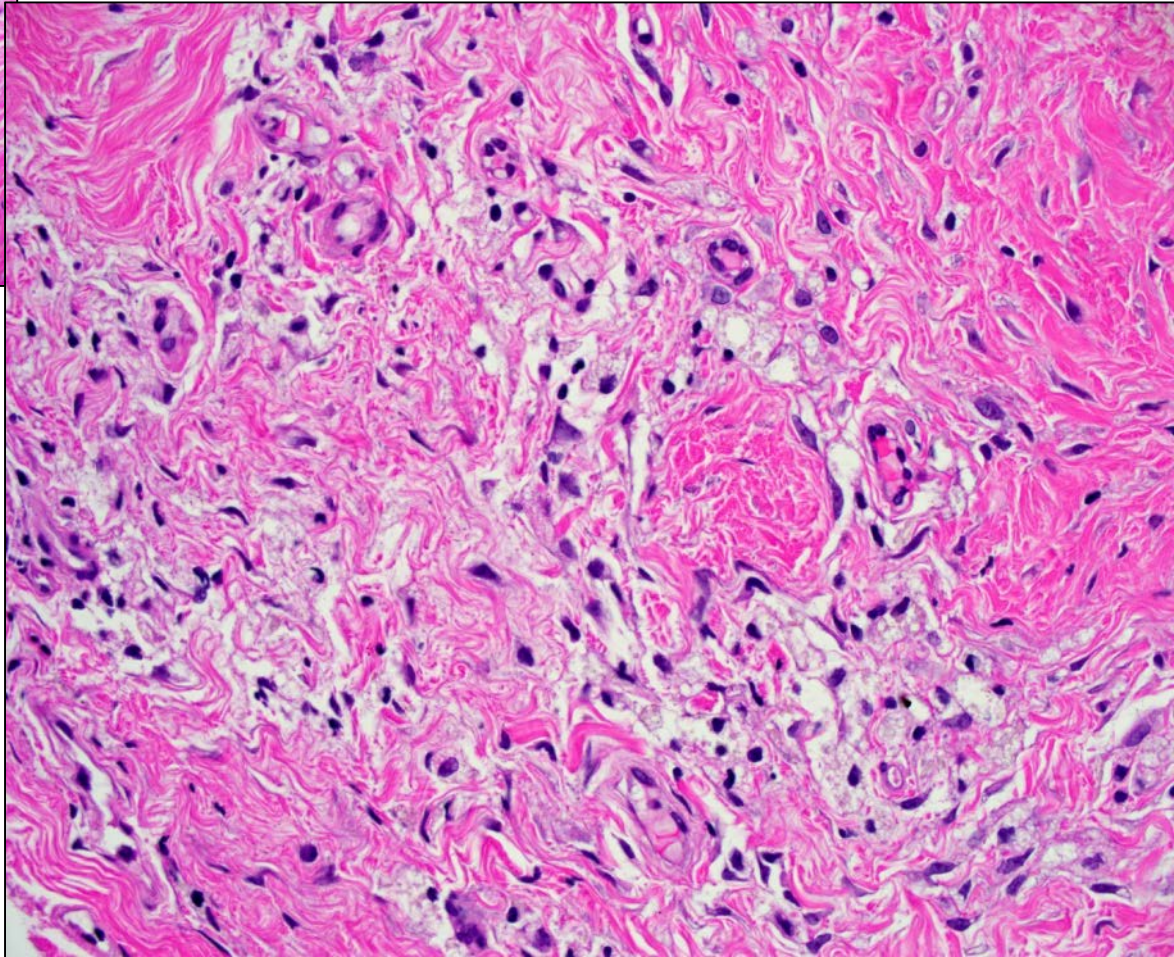
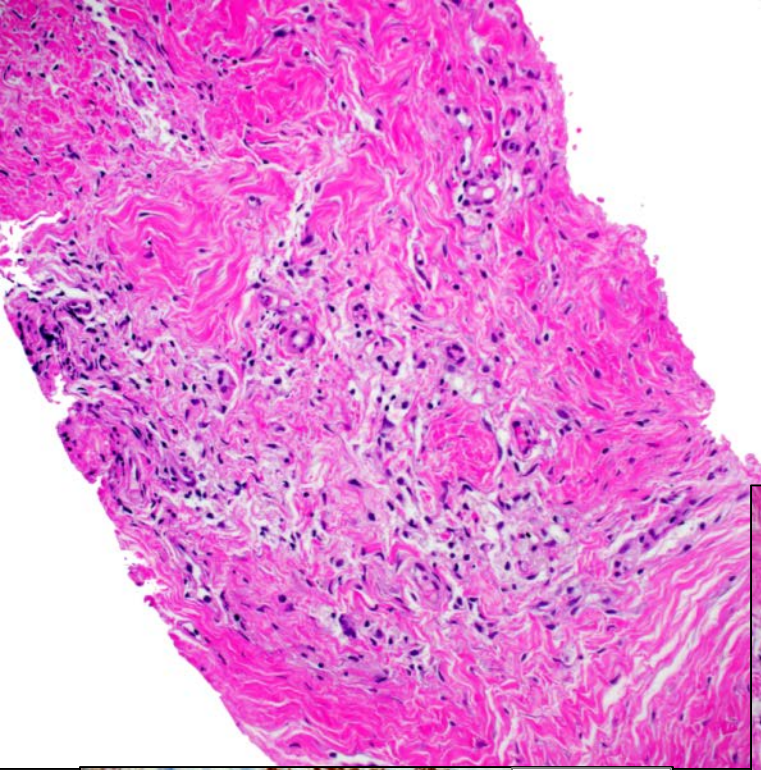


2nd skin lesions with XG
phenotype and *BRAF*-V600E+
prompted ECD workup

Johnson et al. J Cutan Pathol. 2015.
Mar;43(3):270-5.

38 yo F with both skin LCH and ECD

3rd bx: Retroperitoneal biopsy



F13a

Erdheim Chester Disease (ECD)

- **MIP*** - *Foamy CD68 histiocytes ≠ ECD*
 - Clinicoradiographic correlation with xanthogranuloma phenotype is important
 - Molecular as an additional diagnostic aid
- **Updates to proposed classification**
 - *BRAF* and beyond
 - Myeloid inflammatory neoplasia
 - “L” group lesion with XG immunophenotype
 - LCH
 - ECD (Erdheim Chester Disease)
 - Mixed LCH/ECD
 - ICH (indeterminate cell histiocytosis)

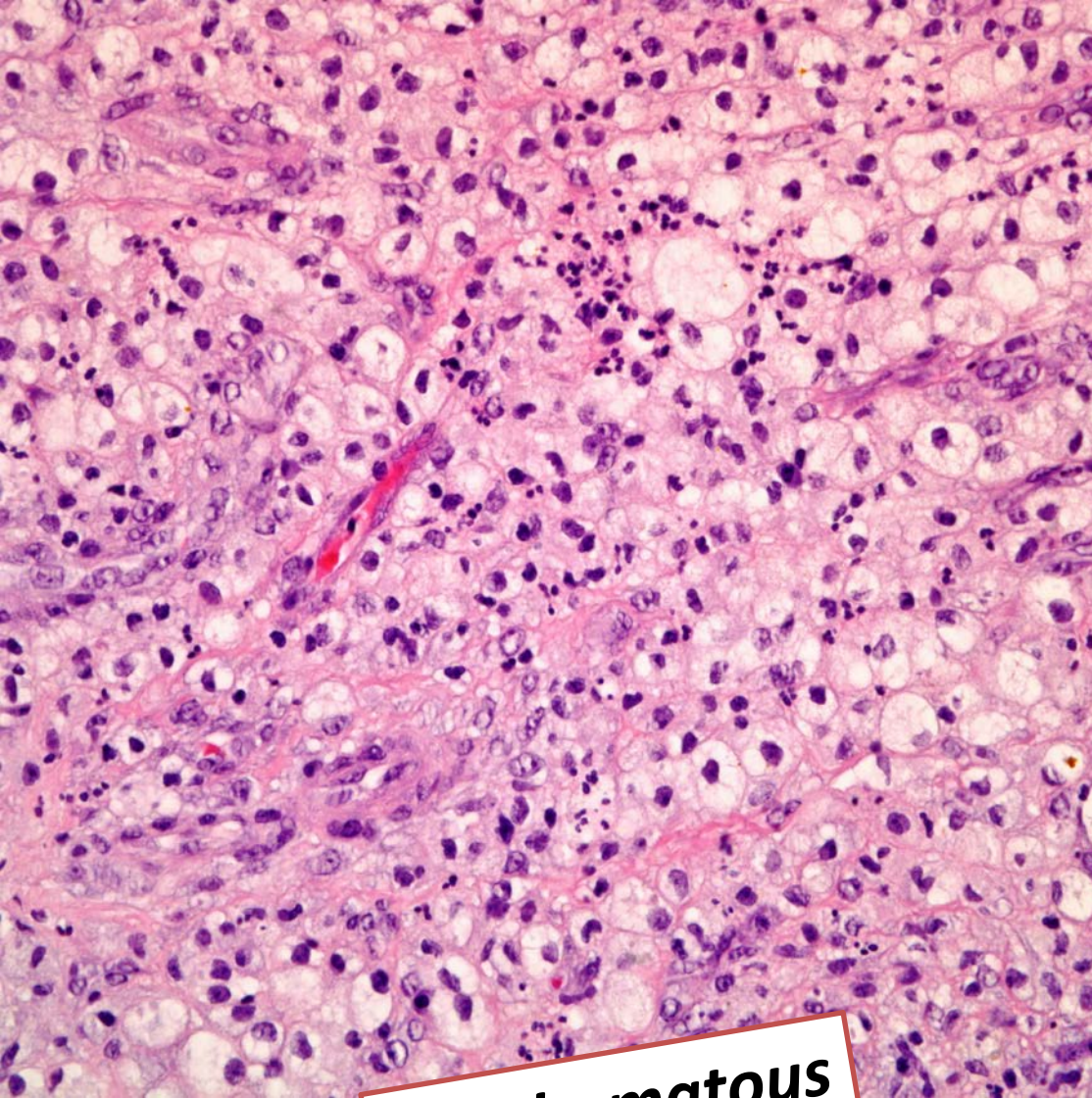
ECD = Clinical, Radiographic, and Pathologic

| Organ system involvement | |
|--------------------------|--|
| Skin ^{24,95} | Xanthelasma Yellow or red-brown plaques |
| Heart ¹⁵ | Pericardial effusion Myocardial infiltration, right atrial mass Periaortic sheathing ("coated aorta") |
| Lungs ^{43,96} | Interlobular septal thickening, ground-glass or centrilobular opacities on CT |
| Retroperitoneum | Perinephric infiltration |
| Liver and spleen | Rare |
| Bone ³³ | Femurs and tibia Bone pain |
| Lymph nodes | Reported, but uncharacteristic |
| CNS ^{48,97,98} | Cerebellar or brain stem lesions Dural-based lesions Brain parenchymal lesions |



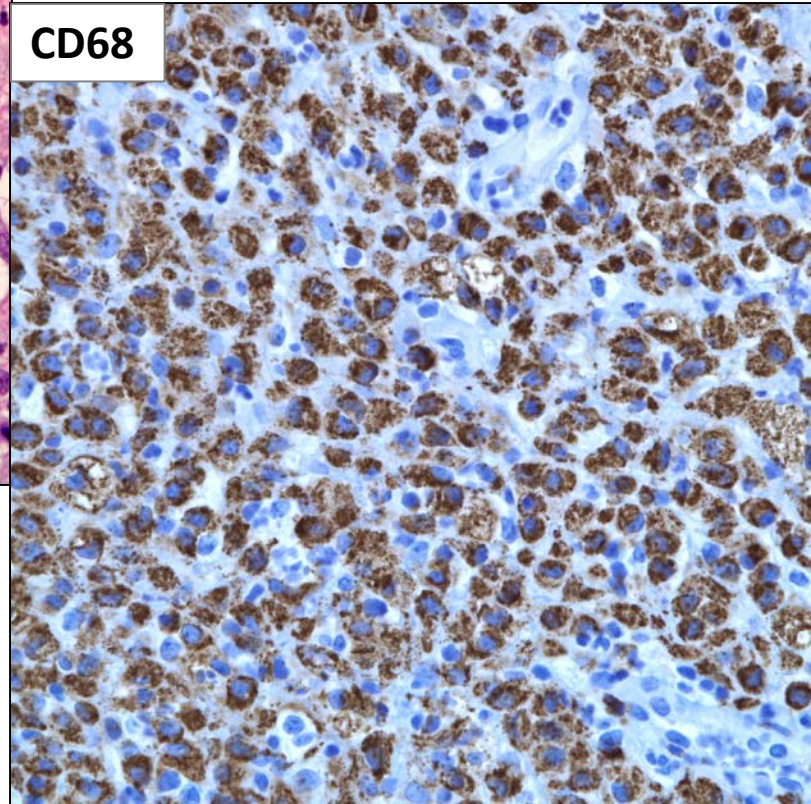
PET

⁹⁹Tc

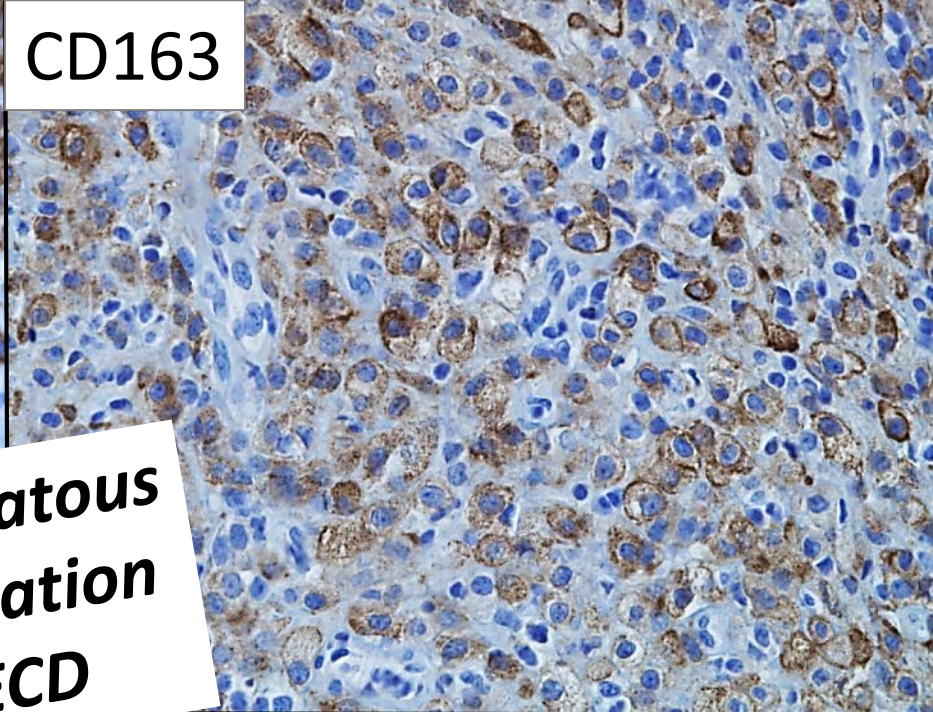
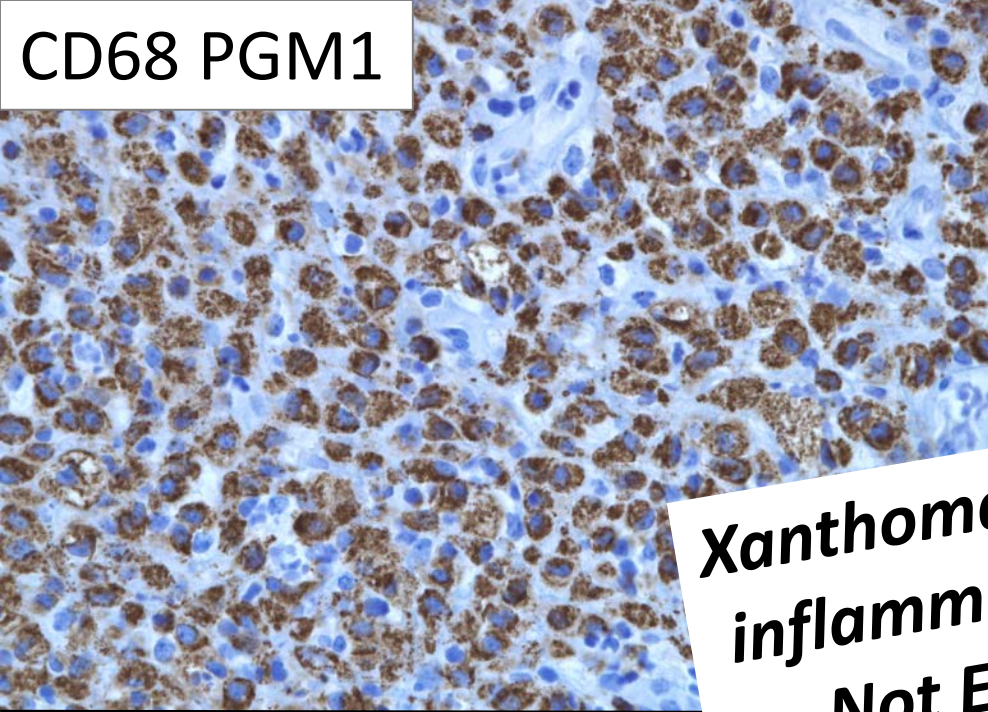


CD68+
Xanthomatous
histiocytes ≠
ECD

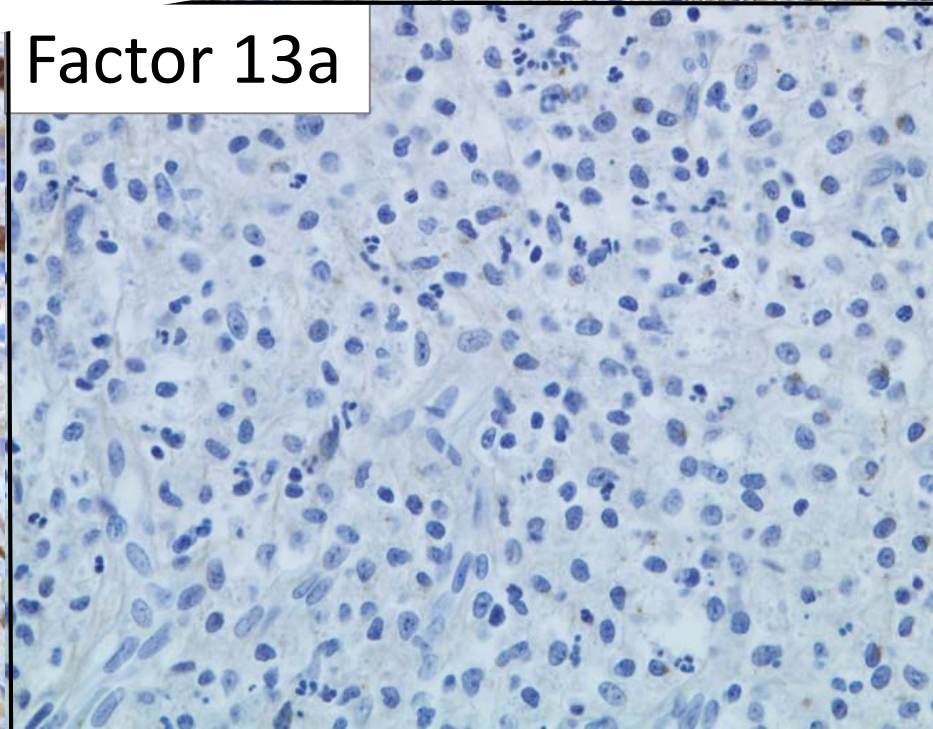
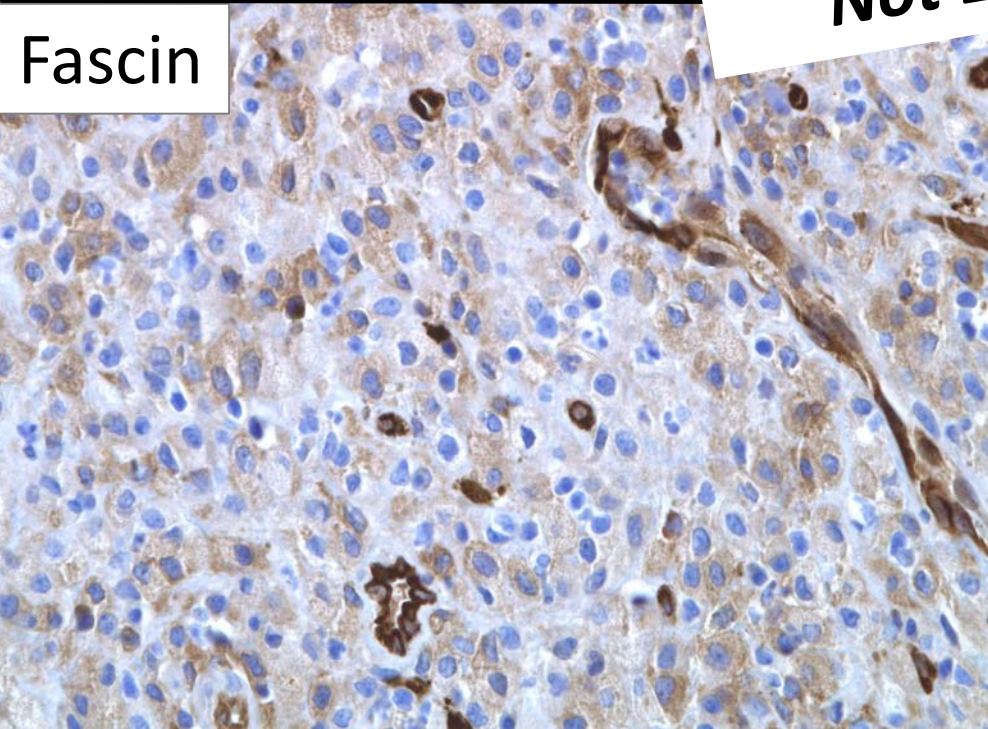
CD68



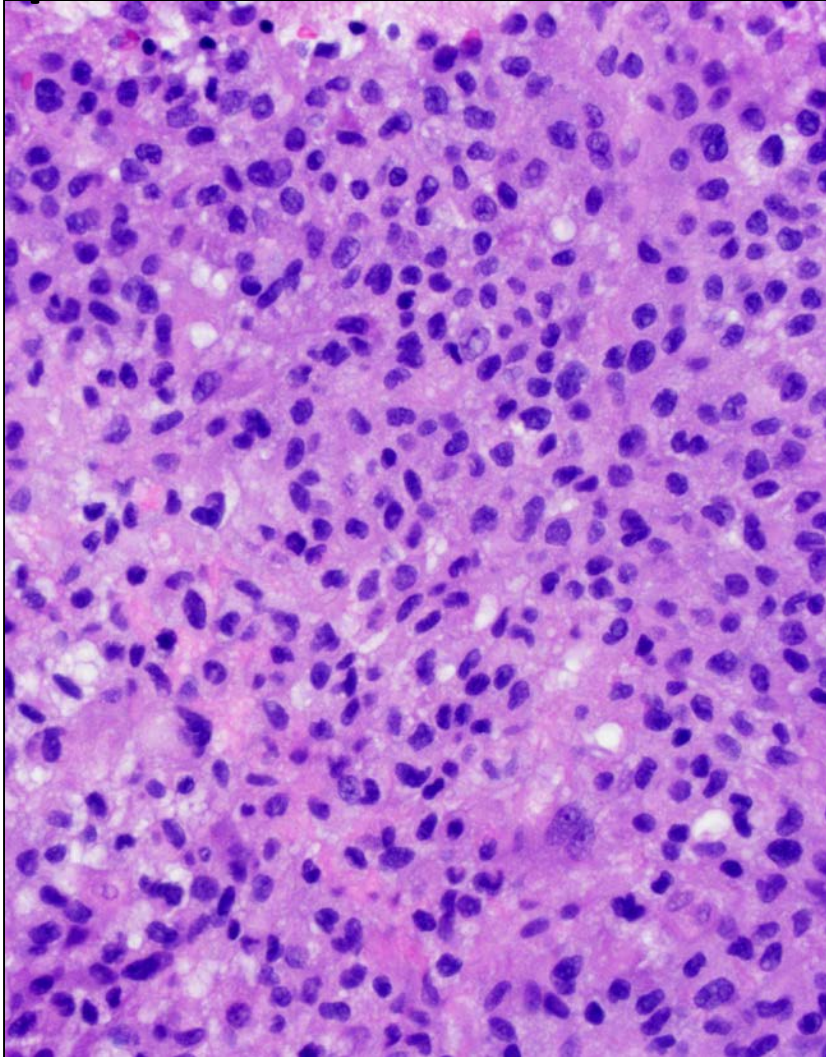
**Xanthomatous
inflammation
Not ECD**



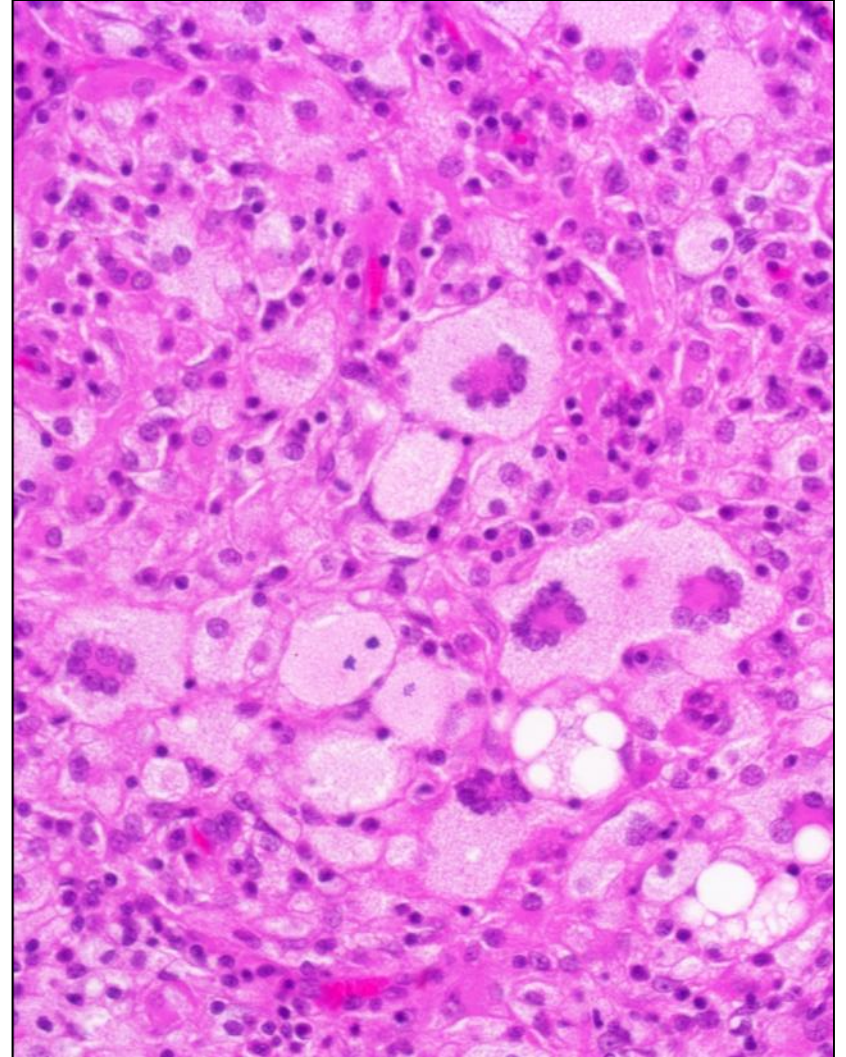
**Xanthomatous
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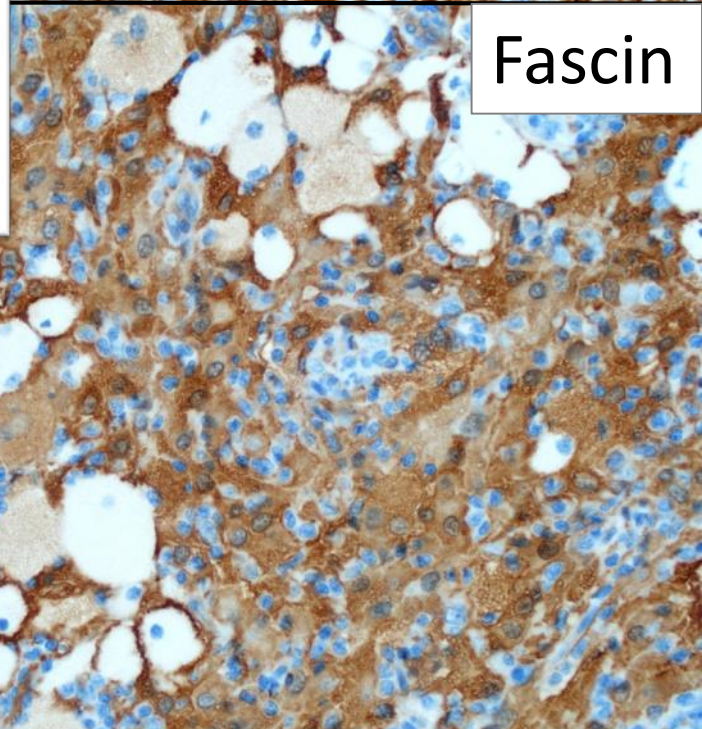
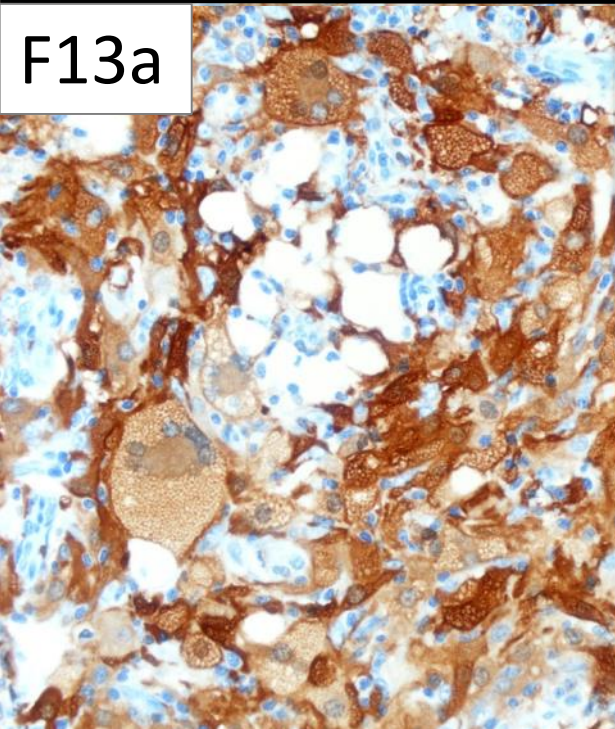
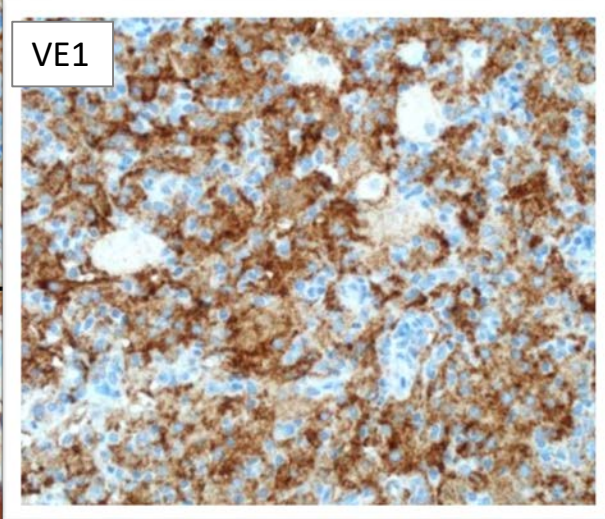
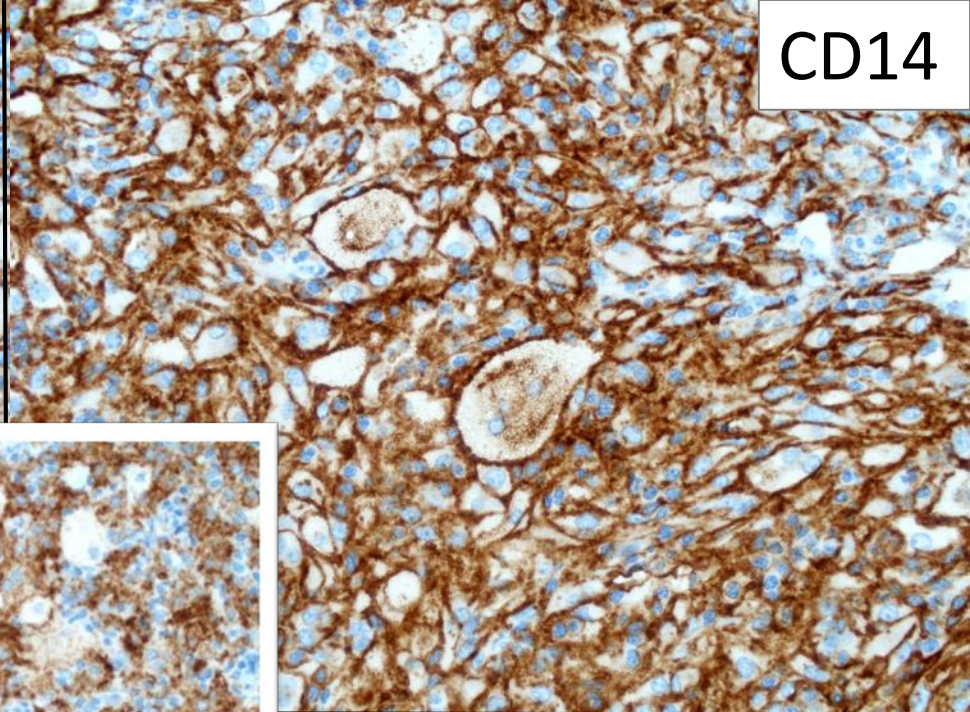
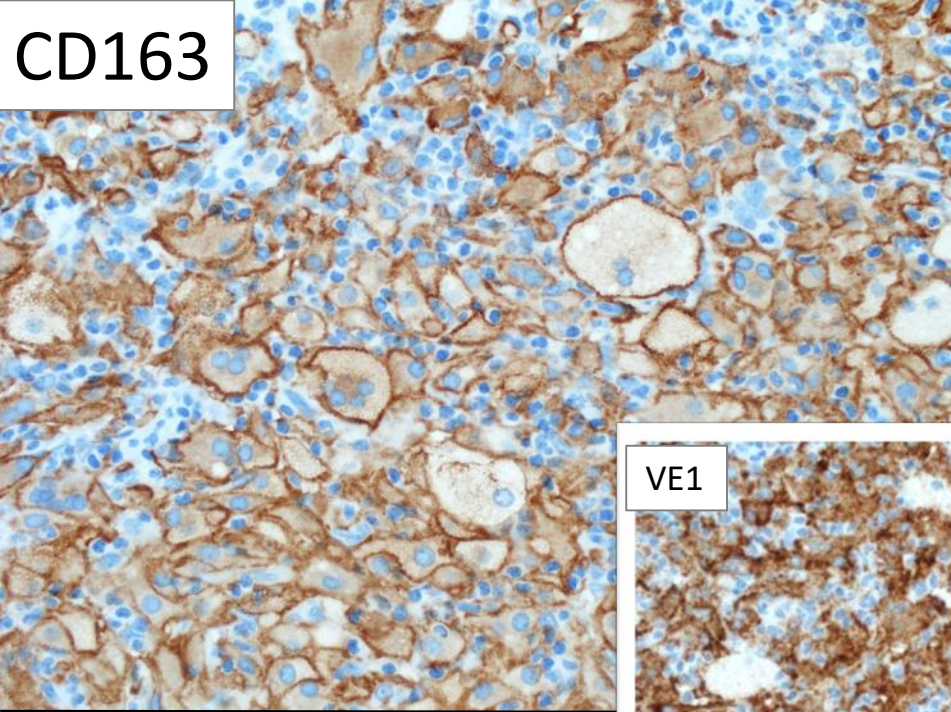


ECD with
pericardial and
pleural effusions



ECD with brain
involvement

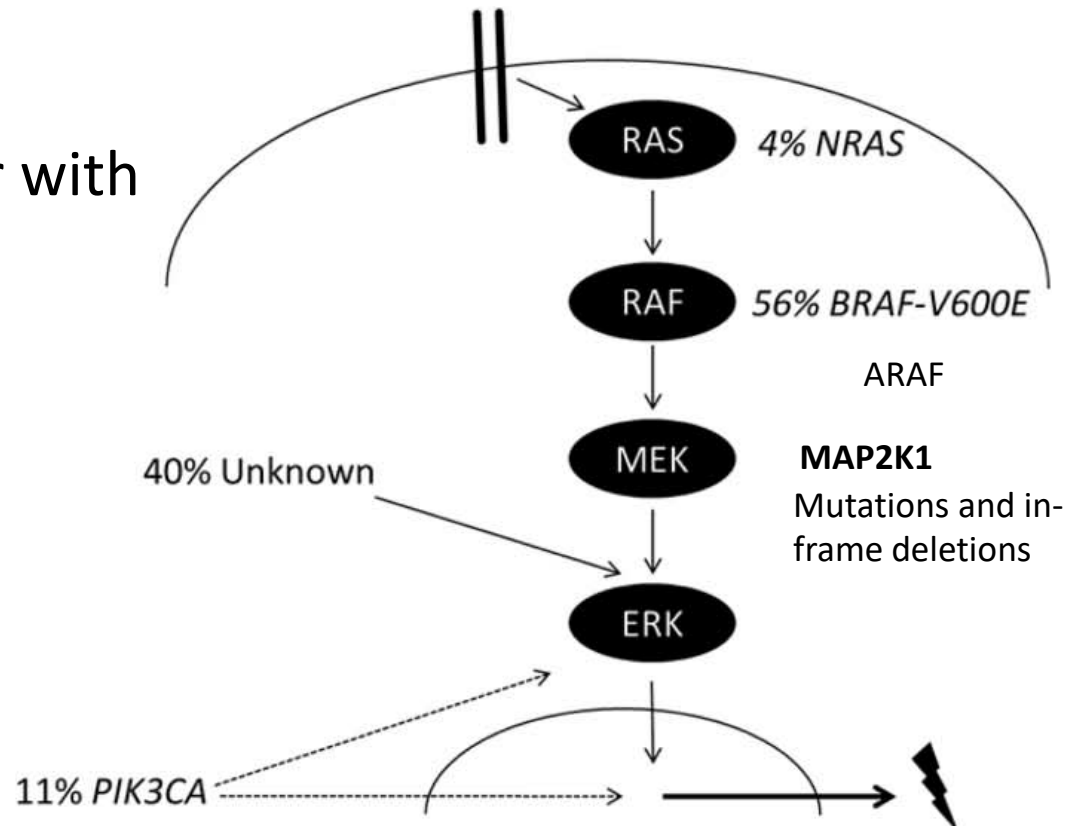




BRAF and beyond ...ECD

- *BRAF-V600E*: Highly dependent of the method of testing: **Highly sensitive PCR methods are recommended in order to detect small allelic fractions** (~1% mutant)

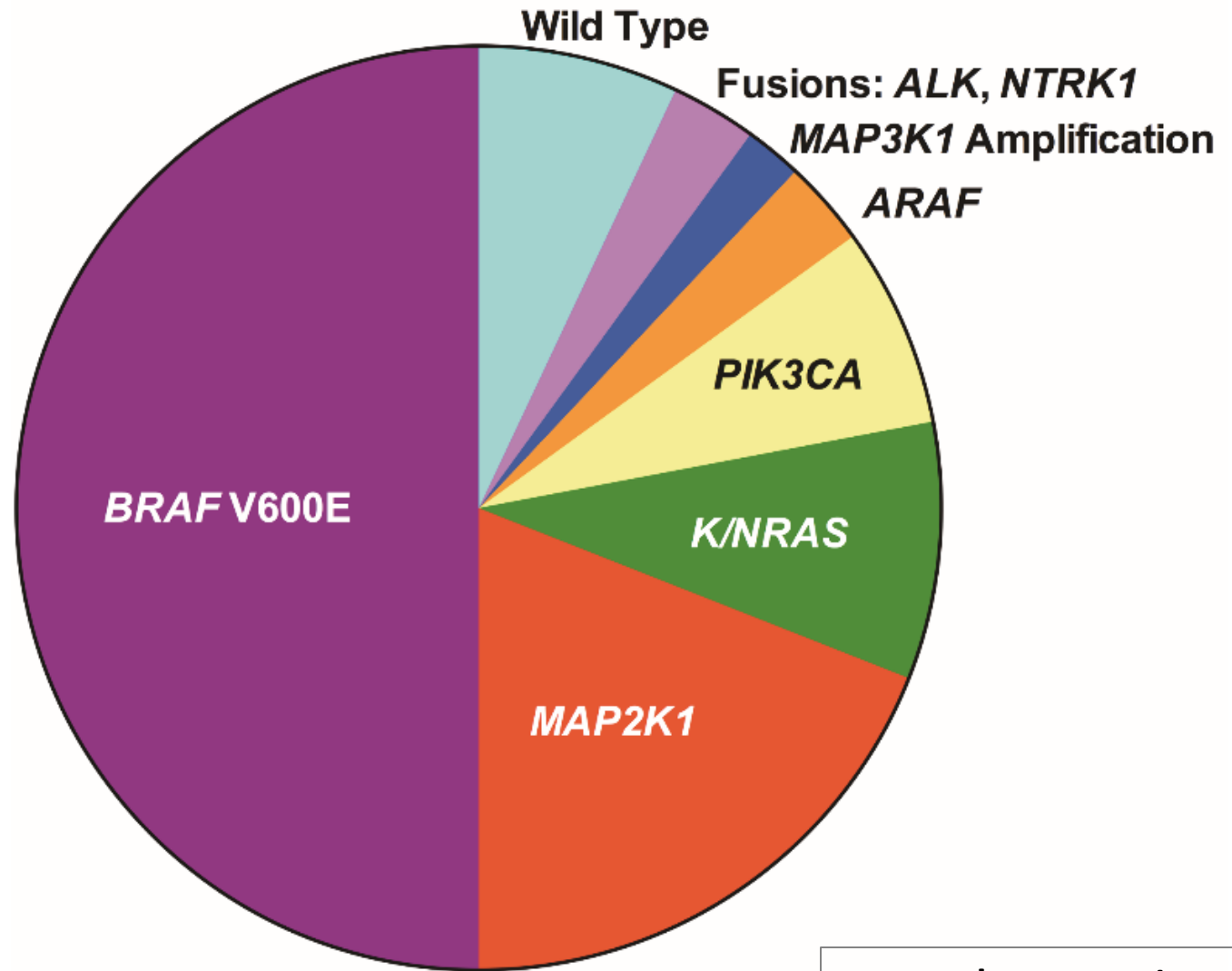
- *BRAF-V600E* can co-occur with *ARAF*, *PIK3CA* mutations
- New targetable kinase gene fusions*
 - *KIF5B-ALK*
 - *LMNA-NTRK1*



*Diamond EL, Durham BH, et al.
Cancer Discovery. 2016;6(2):154-65.

Allen CE, Parsons DW. Hematology Am Soc Hematol Educ Program. 2015;2015:559-64.

Diverse Kinase Alterations in ECD:



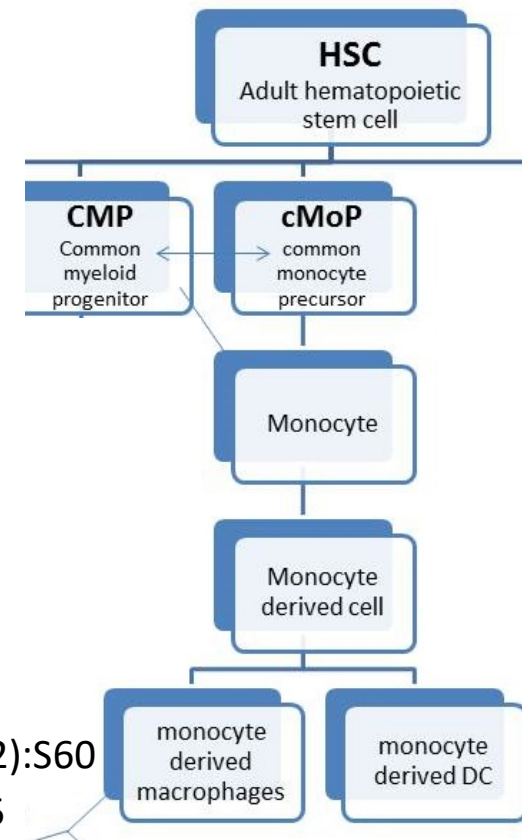
Haroche, *et al. Blood* 2012
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Image courtesy of :
Benjamin H. Durham, M.D.,
Genomic Pathology Research
Fellow in Molecular Oncology
Department of Pathology
Memorial Sloan Kettering
Cancer Center

L group lesion: Both ECD and LCH Inflammatory myeloid neoplasms?

- *BRAF-V600E* expressed in lesional cells along w/ BM progenitor cells and circulating monocytes/myeloid DC*
- Gene expression profiles may still support their divergent morphology/immunophenotype
 - LCH from dendritic cells
 - ECD from monocytes



Diamond EL, Durham BH, et al. *Cancer Discovery*. 2016;6(2):154-65.

33rd annual Histiocyte Society meeting

Singapore October 2-4, 2017

- Become a member of the Histiocyte Society!
 - <https://histiocytesociety.org>
- The **North American Consortium for Histiocytosis (NACHO)** is the first Multi-Institutional consortium in North America with a solid scientific agenda and the research infrastructure necessary for the development and effective implementation of clinical and translational studies and biological research for histiocytic diseases.
 - <http://www.nacho-consortium.org/>
- **The steps to join NACHO and open the LCH-IV are outlined:**
 - <http://www.nacho-consortium.org/openinglch-iv.html>.



International Rare Histiocytic Disorders Registry (IRHDR)



- JXG family, ECD, Multifocal Reticulohistiocytosis, RDD and the Malignant lesions of histiocytic phenotype

<https://clinicaltrials.gov/ct2/show/NCT02285582>

- More information on HS website:

<http://histiocytesociety.org/main-website-pages/clinical-trials/clinical-studies/IRHDR>