HISTIOCYE NEOPLASMS

Paul C. Hendrie MD PhD

Fred Hutch Cancer Center

Disclosures

- Board Member Erdheim-Chester Disease Global Alliance

Objectives

- Identify the different types of histiocytic diseases
- Identify the common presentations of the histiocytic diseases
- Be able to recommend appropriate interventions & treatments for patients with histiocytic diseases

Langerhans cell histiocytosis

Erdheim-Chester Disease

Rosai-Dorfman-Destombes Disease

See in Onc clinic or refer to Rheum?

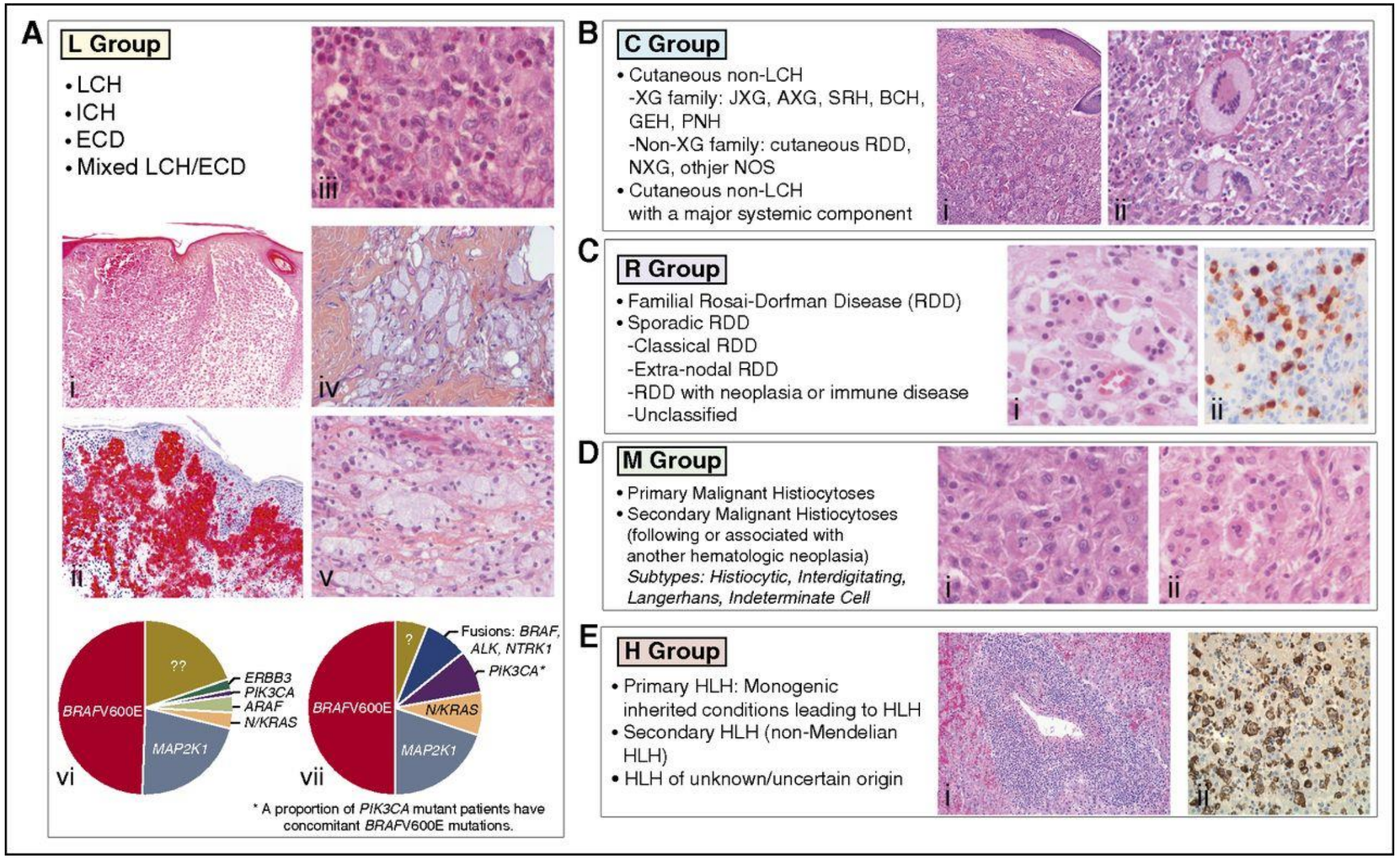
HISTIOCYTE NEOPLASMS

- **Hematologic** disorders characterized by the accumulation of **neoplastic myeloid**-dendritic cell (**antigen presenting**) cells with an accompanying **inflammatory infiltrate**
- **Rare**, less than 1% of cancers of the soft tissue and lymph nodes.
- Presentation varies from localized and mild to disseminated and lethal.
- Nonspecific presentations often lead to a significant delays in the diagnosis and treatment
- Patients should ideally be evaluated and treated at centers of expertise.

HISTIOCYTE NEOPLASMS

- There are over 100 subtypes of histiocytoses.
- Working Group of the Histiocyte Society in 1987, 3 groups:
  - Langerhans cell, non-Langerhans cell, and malignant histiocytoses.
- In 2016 Histiocyte Society published a revised classification based on clinical, radiographic, histologic, phenotypic, and other molecular features, dividing them into five groups:
  - 1) Langerhans related
  - 2) cutaneous and mucocutaneous
  - 3) malignant histiocytosis
  - 4) Rosai-Dorfman disease (RDD) and
  - 5) hemophagocytic lymphohistiocytosis and macrophage activation syndrome.

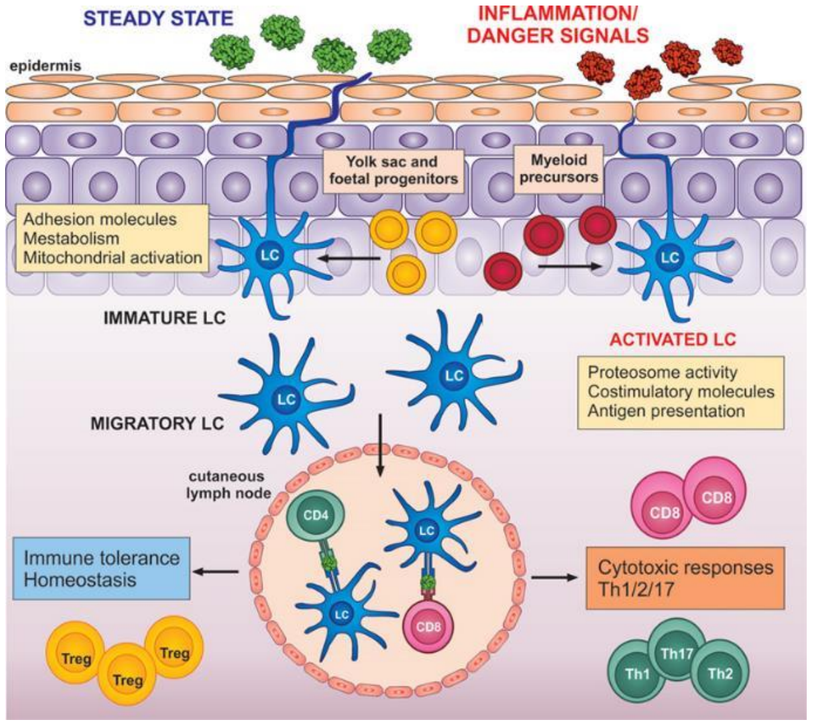
HISTIOCYTE NEOPLASMS



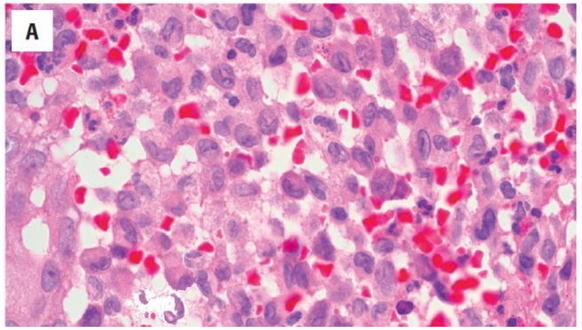
Jean-François Emile et al. Blood 2016;127:2672-2681

Langerhans Cell Histiocytosis

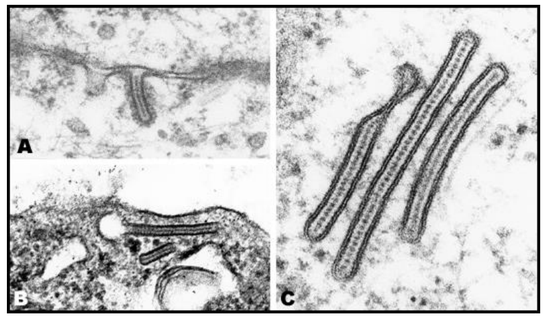
- Initially categorized as an immunologic inflammatory disease (not a neoplasm) based on the appearance of the lesions with a mixed inflammatory infiltrate and went by many names including Histiocytosis X
- Renamed Langerhans cell after Nezolof observed Birbeck granules in the lesion histiocytes in 1973.
- Now we stain for the lectin langerin to identify cells that make Birbeck granules



Bennett C.L., et. al., Front. Immunol., 29 November 2017



Picarsic, J.L. and Chikwava, K. from *Hematopathology*, 3rd ed. 2018



British Journal of Haematology, 2002, 116, 3-9

Langerhans Cell Histiocytosis

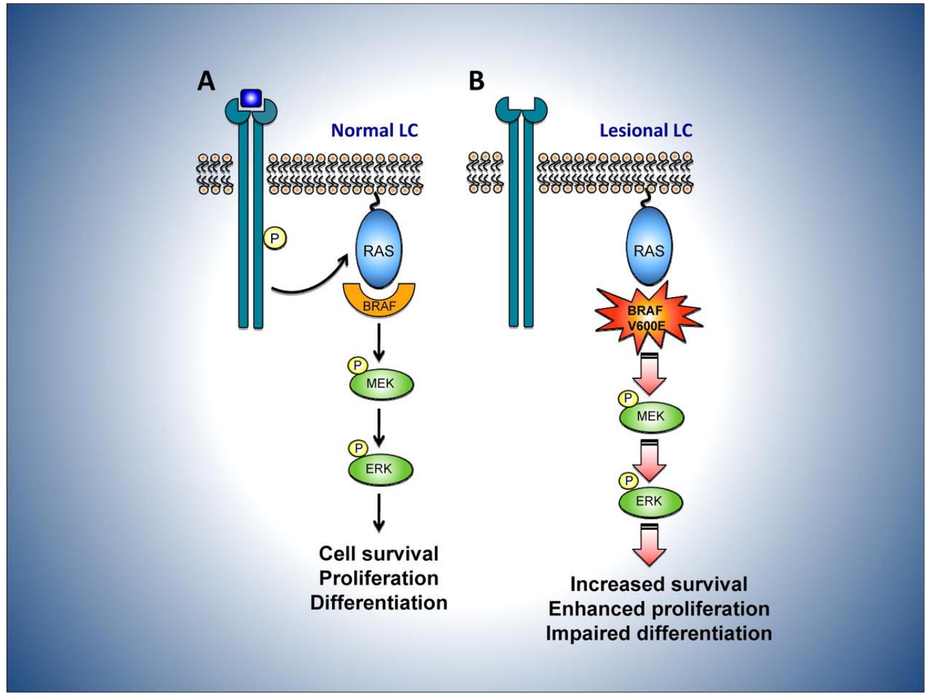
Brief report

Recurrent *BRAF* mutations in Langerhans cell histiocytosis

Gayane Badalian-Very,[1-3] Jo-Anne Vergilio,[4,5] Barbara A. Degar,[6-8] Laura E. MacConaill,[9] Barbara Brandner,[1-3] Monica L. Calicchio,[4] Frank C. Kuo,[5,10] Azra H. Ligon,[5,10,11] Kristen E. Stevenson,[12] Sarah M. Kehoe,[9] Levi A. Garraway,[1-3,9,13] William C. Hahn,[1-3,9,13] Matthew Meyerson,[1,2,9,13] Mark D. Fleming,[4,5] and Barrett J. Rollins[1-3]

Badalian-Very G. et. al., Blood. 2010 Sep 16;116(11):1919-23.

The presence of recurrent activating mutations in the MAPK pathway (including the common BRAF V600E mutation found in other cancers) in the majority of LCH cases supports the current classification as a neoplastic process



Kim E. Nichols, and Robert J. Arceci Blood 2010;116:1825-1827

Langerhans Cell Histiocytosis

- Most common histiocytic disorder.
  - 5 to 9 cases per 1 million in children (>15 years)
  - 1 case per 1 million in adults (>15 years).
- Most cases are mild and asymptomatic but can present as rapidly progressing and/or disseminated life-threatening disease.
- Common sites of involvement:
  - bone, skin, pituitary gland, liver, spleen, bone marrow, lungs, and lymph nodes.
- A pulmonary form of LCH can occur in adults and is associated with smoking.
- Solitary or multifocal bone lesions
- Endocrinopathy is common especially diabetes insipidus (DI), more commonly with multisystem disease.
- CNS involvement is most often with multi-system disease but can present as a solitary lesion
- High prevalence of concomitant and subsequent malignancies, especially myeloid malignancies

LCH Diagnostic Evaluation

- A detailed review of symptoms and physical examination
- Comprehensive neurocognitive and psychological assessments are also recommended in select patients.
- Whole body PET/CT is recommended for the staging of LCH. FDG-PET/CT is superior to other cross-sectional imaging techniques for detection of sites of active LCH, with the exception of pulmonary lesions
- For suspected pulmonary disease
  - High-resolution chest CT recommended
  - Pulmonary function testing should be performed
  - and Echocardiogram to screen for pulmonary hypertension
- MRI of the brain is recommended even in the absence of neurologic or endocrine abnormalities.
  - “loss of bright spot” in pituitary can be seen with diabetes insipidus

LCH Diagnostic Evaluation

- Laboratory tests should include:
  - complete blood count (CBC), blood chemistry, coagulation studies, thyroid-stimulating hormone (TSH), free T4, urinalysis, C-reactive protein, and morning serum cortisol with ACTH.
  - Select patients: prolactin and insulin-like growth factor-1 (IGF-1), follicle-stimulating hormone/luteinizing hormone (FSH/LH) with testosterone and estradiol as clinically indicated.
- Bone marrow evaluation should be performed in all patients with abnormal CBC to rule out marrow involvement of LCH and a concomitant myeloid neoplasm.

LCH Diagnostic Evaluation

- Biopsy of tumor tissue is recommended in all cases.
  - LCH cells are mononucleated, typically with a coffee bean-shaped nucleus, Abundant eosinophils and multinucleated giant cells are frequent. Fibrosis may be present.
  - LCH neoplastic histiocytes a positive for CD1a, CD207 (langerin) and S100.
  - Cyclin D1 can be helpful for differentiating neoplastic Langerhans cells from reactive Langerhans cell proliferation.
  - CNS lesions show CD8+ lymphocytes and often lack CD1a-positive histiocytes.
  - Birbeck granules can be identified by electron microscope(rarely done).
  - BRAF V600E (VE1) IHC is recommended on all tissue biopsy samples,

LCH Diagnostic Evaluation

- BRAF V600E allele-specific PCR is recommended if IHC is unavailable or when BRAF V600E (VE1) IHC results are equivocal or negative.
  - BRAF V600E is present in 38% to 64% of LCH cases
- A comprehensive NGS panel including other genes in the MAPK pathway (ie, ARAF, NRAS, KRAS, MAP21K, PIK3CA) should be performed in patients with BRAF wild-type disease.
  - MAP2K1 mutations are present in ~20% of LCH cases
  - Activation of RAS-RAF-MAPK pathway is universally present

LCH Treatment

Unifocal and single system disease without critical organ involvement

- Observation for asymptomatic lesions-spontaneous regressions has been reported
- Limited curettage for isolated bone lesions, avoid large surgeries and disfigurement
- Steroid injections, after curettage
- Radiation therapy, up to 3 bony lesions (10-20 Gy)
- For skin,
  - Topical steroids or mechlorethamine
  - Psoralen with ultraviolet A and narrow band ultraviolet B
  - Oral low dose methotrexate or hydroxyurea

LCH Treatment

Multifocal or Multisystem Disease or Unifocal with critical Organ Involvement

- Pulmonary LCH may resolve with smoking cessation
- High-dose prednisone (1 mg/kg/dy X 1 month) for pulm LCH
- Bisphosphonates or Indomethacin for multifocal bone disease
- Vinblastine and prednisone is only indicated in children, not adults
- Cytarabine 100 mg/m2/dy X 5 dys (may increase to 150 mg/m2 for CNS disease) repeated monthly for up to 12 months
- Cladribine also 5 dy regimen repeated monthly for 4 to 6 months
- Combination cytarabine with cladribine or methotrexate
- For skin, may consider thalidomide or lenalidomide

LCH Targeted Therapy

- BRAF and MEK inhibitors are promising and effective treatment for LCH but there is not universally agreement on when they should be used
- For BRAF V600E and other susceptible BRAF mutations, vemurafenib or dabrafenib can be used.
  - Toxicities include hypertension, rash, increase lipase, hyperkeratosis, actinic keratosis, fatigue
- For patient with resistant BRAF mutations or wild type BRAF, the MEK inhibitors cobimetinib and trametinib are effective
  - Toxicities include decrease ejection fraction, rash, diarrhea, fatigue
- Combinations of BRAF and MEK inhibitors have also been used

LCH Follow Up

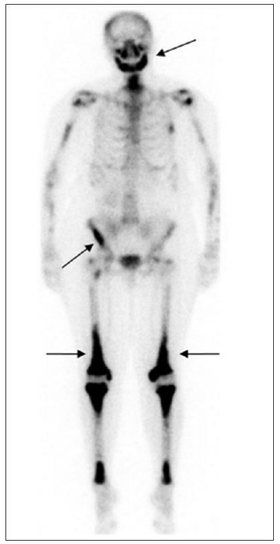
- Disease response is usually assessed after 2 – 3 cycles of systemic therapy with a PET/CT, CT or MRI and at the end of treatment
- Most relapses occur within the first 2 years
  - Recommend imaging surveillance every 3-6 months X 2 yrs
  - After 2 yrs, imaging performed at most annually
- Pulmonary function testing should be done for pulmonary LCH
- Bone marrow evaluation in setting of cytopenias or leukocytosis
- On BRAF inhibitors, skin exams and ECG
- Endocrine evaluations every 1 to 2 years

Erdheim-Chester disease (ECD)

- ECD is a rare histiocytic neoplasm, with approximately 800 cases having been reported as of May 2020.45
  - An increase in detection of cases has been observed more recently, potentially due to improved recognition of this disease through imaging and pathology.
- Like LCH, ECD is a clonal disorder of dendritic cell/histiocytes.
- Morphology of the infiltrating cells are quite different, with foamy CD68 positive and CD1a negative cells.
- ECD predominantly affects adults, with a median age of approximately 45 years in the United States, more common in men than women.
- ECD is rarely observed in children.
- Mixed ECD/LCH is fairly common, with LCH lesions reported in 20% of patients with ECD.

ECD: Clinical Presentation

- Usually more than one system
- Radiotracer uptake in long bones, most common
- Retroperitoneal involvement ‘hairy kidney’
- Heart involvement, pericardial disease (poor prognosis), periarterial fibrosis of aorta “coated aorta”
- Lung involvement
- Brain disease/cerebellum and brain stem-worse prognosis (15-55%)-increased risk for stroke
- Skin/eyelids-xanthelasma
- Eyes and orbits-exophthalmos
- Pituitary gland/diabetes insipidus
  - Hyperprolactinemia, hypogonadism, adrenal insufficiency, hypothyroidism
- Concomitant myeloid neoplasm (3-10%)

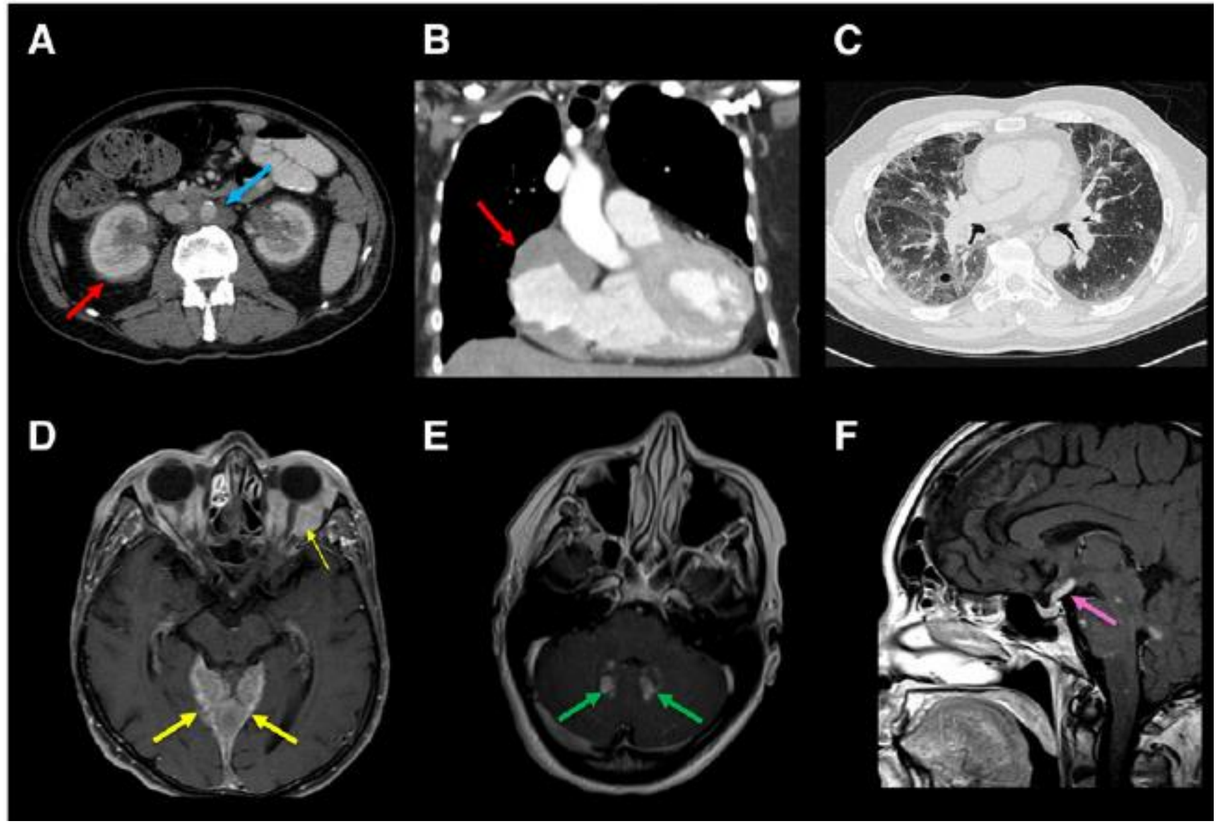


Martineau P, Pelletier-Galarneau M, Zeng W. The imaging findings of erdheim–chester disease: A multimodality approach to diagnosis and staging. World J Nucl Med 2017;16:71-4

Kim et al 2010 Ann Derm 22

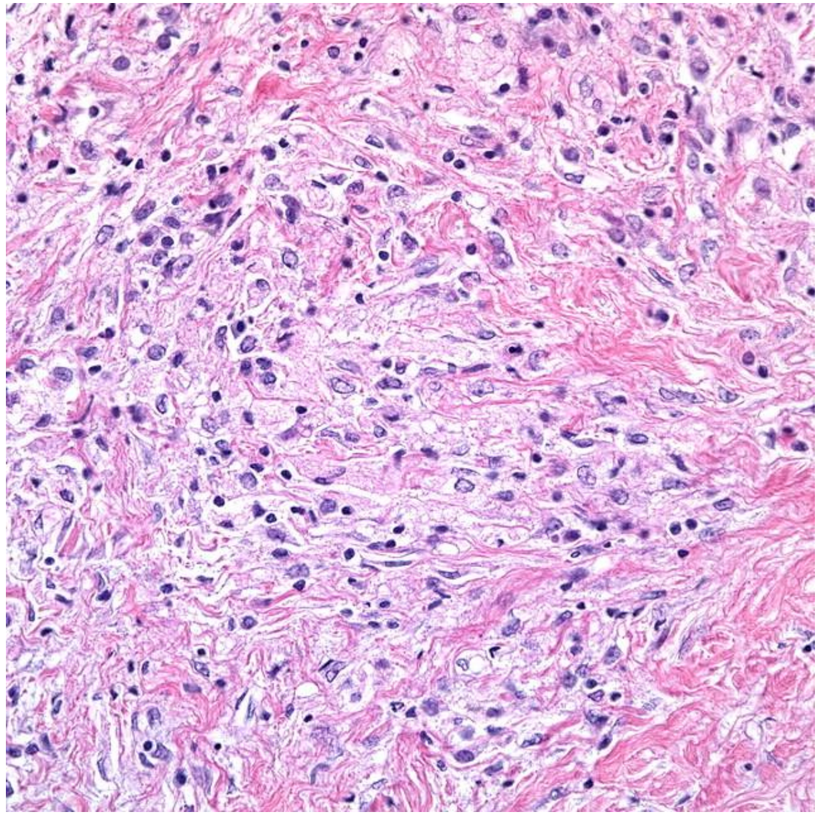
ECD-Baseline clinical evaluation

- Comprehensive ROS and physical exam
- Neurocognitive and psychological assessments
- Whole body PET/CT
  - Preferred to bone scan
- Brain MRI
- CT chest and abdomen
- ECHO and cardiac MRI



Diamond et 2014 Blood 124(4)

ECD-Baseline clinical evaluation

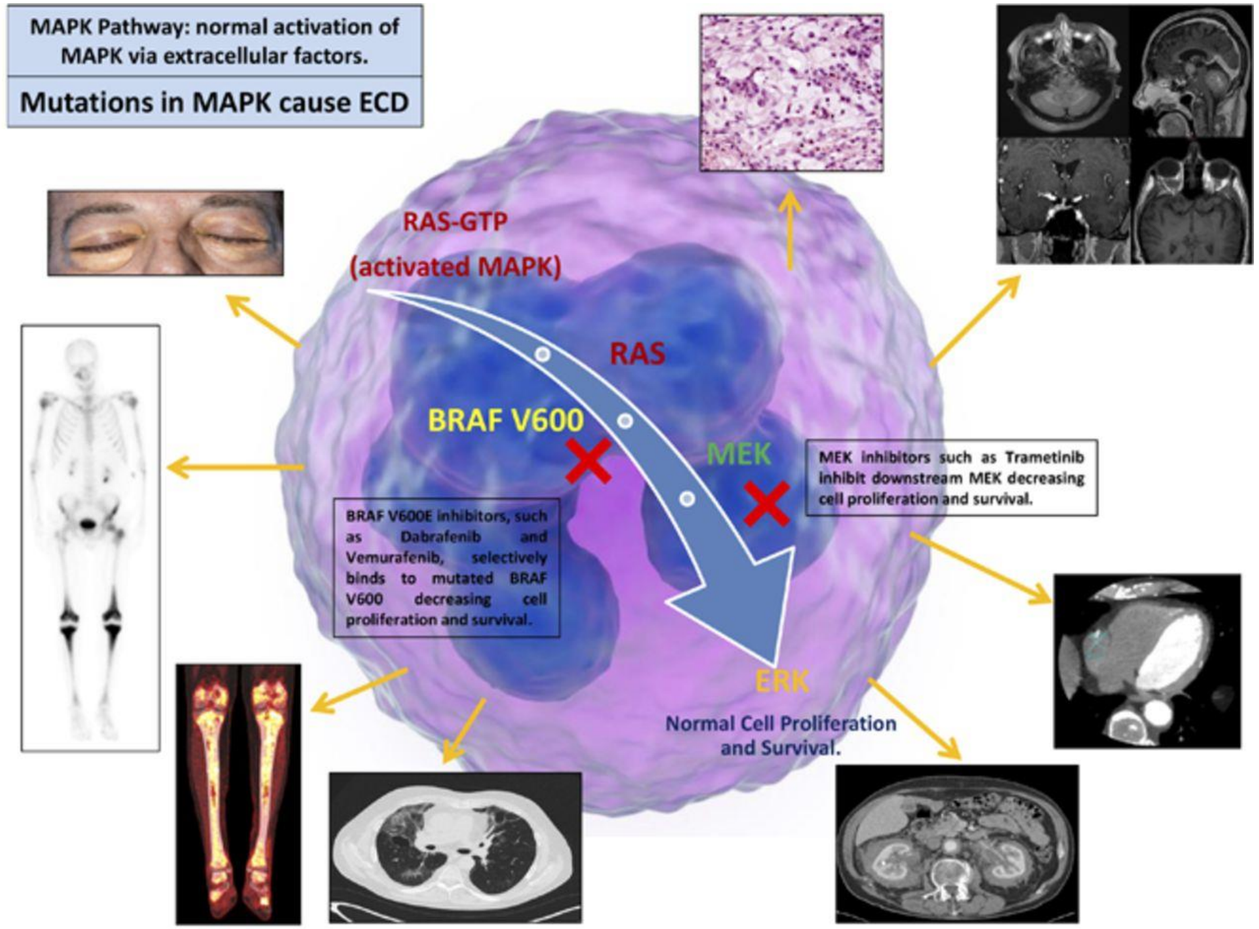


Carl E. Allen, and Kenneth L. McClain Blood 2011;117:2745-2746

- Laboratory evaluation
  - CBC, chemistry, CRP, coagulation studies, TSH, free T4, morning urine and serum osmolality, morning serum cortisol with ACTH, prolactin, IGF-1, FSH/LH with testosterone and estadiol
  - Bone marrow biopsy for CBC abnormalities
- Tissue biopsy
  - foamy mononucleated histiocytes with a small nucleus, surrounding fibrosis, xanthogranulomatosis, and Touton giant cells.
  - CD68-positive, CD163-positive, CD14-positive, factor XIIIa-positive, CD1a –negative, langerin negative
  - BRAF V600E (VE1) IHC
  - NGS for mutation in MAPK pathway

ECD-mutations

- Somatic mutations contributing to ECD partially overlap with that of LCH.
- BRAF V600E activating mutations are present in 38% to 68% of ECD cases.
- Other prevalent gene mutations in ECD include MAP2K1, ARAF, NRAS, KRAS, and PIK3CA
- CSF1R mutations and BRAF, ALK, and NTRK1 fusions are found in a small number of ECD cases.



Juvianee I. Estrada-Veras et al. Blood Adv 2017;1:357-366

ECD Treatment

- Observation is appropriate for patients with asymptomatic limited disease
- Targeted agents are first line therapy for multisystem disease
- Other therapies
  - Interferon alpha-2a or pegylated interferon alpha (may require higher doses for CNS disease)
  - Cladribine
  - Sirolimus plus prednisone
  - Oral methotrexate alone or with prednisone or inflixamab
  - Anakinra (IL-1 receptor antagonist)

ECD Targeted therapy

- For BRAF V600E mutated disease-vemurafenib (FDA approved) or dabrafenib
  - Higher doses for CNS disease
- For BRAF wild type-cobimetinib or trametinib
  - Same concern for toxicities as in LCH

ECD Targeted therapy-special cases

- ECD with ALK fusion-Crizotinib, alectinib, brigatinib, ceritinib, lorlatinib
- ECD with RET rearrangement-selpercatinib
- ECD with activating mutations in CSF-1R-pexidartinib
- ECD with NTRK gene fusions-larotrectinib or entrectinib
- ECD with PIK3CA mutations- mTOR inhibitors such as sirolimus and everolimus

ECD-Follow Up

- PET CT every 3–6 months after starting therapy until stabilization of the disease
- Organ-specific imaging (CT or MRI) every 3–6 months until disease stabilization and then every 6–12 months
- Regular skin examination and ECG for patients treated with BRAF inhibitors
- Monitor every 1–2 years for pituitary hormone abnormalities

BLOOD, 24 JULY 2014 • VOLUME 124, NUMBER 4

HISTIOCYTOSIS ASSOCIATION®
A Rare Community

https://histio.org

NCCN National Comprehensive Cancer Network®

https://www.nccn.org

ERDHEIM-CHESTER DISEASE GLOBAL ALLIANCE

http://erdheim-chester.org

HS HISTIOCYTE SOCIETY

https://histiocytesociety.org

Fred Hutch Cancer Center

Questions?