TREATMENTS

Therapeutic option that is FDA-approved:

BRAF-inhibitor vemurafenib for *BRAF* V600-mutation positive ECD

Therapeutic options under clinical trials include:

BRAF & MEK kinase inhibitors (cobimetinib, dabrafenib, and trametinib)

Therapeutic options used off-label based on anecdotal experience include:

- Interferon-alpha
- Chemotherapy (cladribine, clofarabine)
- Cytokine-targeting medications (anakinra, Actemra, Remicade)
- Immunosuppressants (Rapamune, methotrexate, Cellcept, Imuran)
- Steroids (e.g., prednisone)
- Surgical debulking

PATHOLOGY

Symptoms vary, depending upon the organ(s) involved. Each patient has a different combination of symptoms, making diagnosis difficult. Common symptoms may include:

- Infiltration by foamy or lipid-laden, epithelioid or spindled histiocytes, with associated fibrosis, osteosclerosis and/or inflammatory background; foam cells not always present
- Touton giant cells may be present
- Immunohistochemistry; ECD histiocytes are XG family phenotype:

CD1a-	CD68+	CD163+
Factor 13a+	Fascin+	S-100+/-

- *BRAF* V600E mutations in >50% of patients (tested by PCR or next-generation sequencing)
- Other MAPK pathway alterations, including kinase fusions

NOTE: It is important to rule out concomitant myeloid neoplasms among ECD patients due to their high rates of co-occurrence.

MANAGEMENT

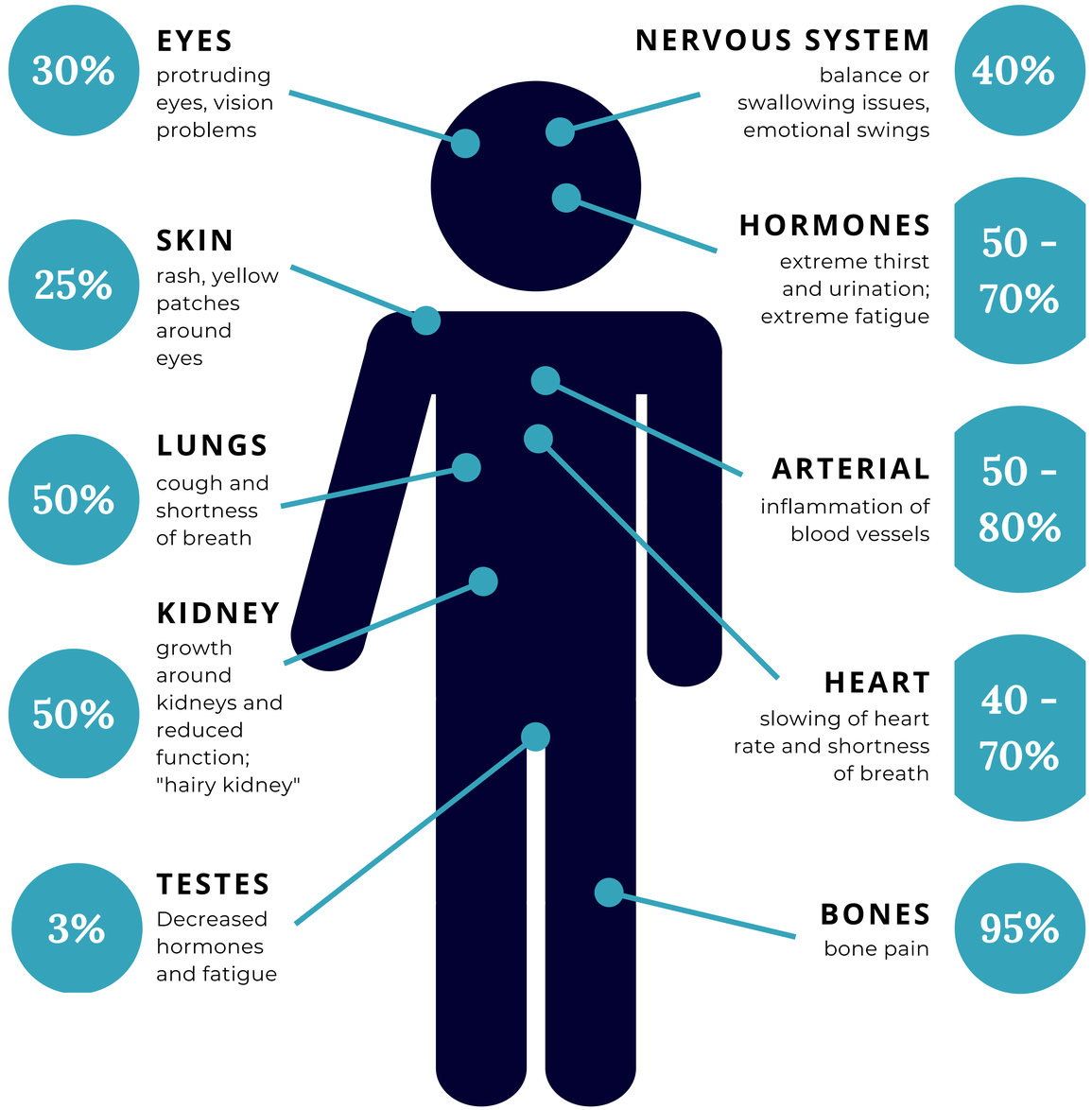
- FDG-PET should be performed every 3-6 months until stabilized
- Organ-specific imaging of affected organs every 3 months until stabilized
- Monitoring of Vitamins B12 & E, and hormones to include testosterone, ADH, thyroid function, insulin, ACTH and PTH
- Initiation of rehabilitation (PT, OT and ST) as warranted
- Currently, most treatment is recommended indefinitely as tolerated

DIAGNOSIS

- Usually diagnosed through biopsy, scans (bone, PET, MRI), and clinical symptoms.
- Bone or PET scan- symmetrical and abnormally increased uptake of the radiotracer in the distal femurs and/or proximal and distal tibia, less commonly in the axial skeleton.
- Important to include vertex to toe regions (not mid-thigh) in PET-scans for capturing bony findings near the knees.
- Cardiac and head MRI are recommended for all patients at the time of diagnosis for comprehensive baseline assessment.

ORGAN INVOLVEMENT

The following diagram shows the percentage of approximately 400 ECD patients who experience issues associated with each of the listed organs. These numbers have been compiled using several existing studies.



Adapted from Goyal G. et al. Mayo Clin Proc. 2019 Aug 28. doi: 10.1016/j.mayocp.2019.02.023

HETEROGENEOUS CLINICAL PRESENTATIONS

Symptoms vary, depending upon the organ(s) involved. Each patient has a different combination of symptoms, making diagnosis difficult. Common symptoms may include:

- Bilateral bone pain in legs and knees
- Constitutional symptoms of weight loss; fever; night sweats; muscle and joint aches; feeling of generalized discomfort, weakness, and fatigue (malaise); flu-like symptoms that linger or continue to return
- Excessive thirst and urination (diabetes insipidus)
- Difficulty walking and balance (ataxia), slurred speech (dysarthria), uncoordinated limb movements (dysmetria) or eye movements (nystagmus)
- Lower back, flank or abdominal pain, often associated with kidney and/or ureter involvement (retroperitoneal fibrosis); reduced kidney function
- Bulging of the eye (exophthalmos/proptosis) and/or vision issues such as double vision (diplopia)
- Sore or bump under the skin, sometimes with a yellow tinge (xanthomas), papular or fleshy rash
- Shortness of breath (dyspnea) Cardiac issues such as heart failure, rhythm abnormalities (particularly bradycardia), pericardial tamponade

ERDHEIM-CHESTER DISEASE REGISTRY

The Registry for Patients with Erdheim-Chester Disease, managed by Memorial Sloan Kettering Cancer Center (MSK), unites leading researchers with patients and physicians like you, who are interested in taking part in building a longitudinal clinical database.

CONNECT WITH THE EXPERTS

An ECD Referral Care Center network is available to treat patients and/or provide consultation to treating physicians when patients cannot travel.

Find more information about these centers at http://erdheim-chester.org/care-centers/.

COMPILED BY LEADING EXPERTS WITHIN THE COMMUNITY OF THE ADVOCACY GROUP

ERDHEIM-CHESTER DISEASE GLOBAL ALLIANCE

A 501(c)(3) non-profit patient advocacy organization supporting those affected by ECD.

Researchers interested in investigating the cause or treatment of ECD are encouraged to contact the organization about possible grant opportunities.

CONTACT US
support@erdheim-chester.org
www.erdheim-chester.org

What is ERDHEIM-CHESTER DISEASE?

INFORMATIONAL GUIDE FOR PHYSICIANS

Erdheim-Chester Disease (ECD)

SIGNS

Depending on organ involvement, some of the following signs may be found.

Moderate anemia, increased creatinine, increased C-reactive protein and erythrocyte pedimentation rate

Bilateral osteosclerosis of the long bones involving the diametaphyseal regions is nearly universal

Strong bilateral long bone uptake of radioactive tracer on 99mTc bone scintigraphs or FDG-PET scans

Infiltrative disease of organs – perinephric stranding or "hairy kidney," peri-aortic infiltrate or "coated aorta," retroperitoneal fibrosis, right atrial infiltration, and pericardial thickening

Interstitial lung disease involving accumulations of histiocytic cells and fibrosis in a predominantly perilymphangitic and subpleural pattern

- A rare non-Langerhans cell histiocytic neoplasm now included under lymphoid malignancies.
- A multisystem disease that can affect virtually any combination of organ systems, including ophthalmic/periorbital, pulmonary, cardiovascular, renal, musculoskeletal, dermatologic, and central nervous system.
- Characterized by excessive production and accumulation of macrophages (histiocytes) within multiple tissues and organs.
- Typical onset between 40 and 70 years of age, although there are documented cases in all age groups; with slight preponderance in males.
- Research suggests that ECD is a clonal hematopoietic disorder, marked by recurrent mutations in the MAP-ERK pathway in all patients. More than 50% of patients have the *BRAF* V600E mutation, and the majority of the remaining patients have other mutations in the MAPK signaling pathway. Chronic uncontrolled inflammation is an important mediator of disease pathogenesis.

Prompt diagnosis and early treatment are critical for more favorable outcomes.