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
- 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 flaky rash
- Shortness of breath (dyspnea)
- Cardiac issues such as heart failure, rhythm abnormalities (particularly bradycardia), pericardial tamponade
- Perilymphangitic and subpleural and fibrosis in a predominantly perimphangitic and subpleural pattern
- Right atrial infiltration, “coated aorta,” retroperitoneal fibrosis
- Reduced kidney function
- Lower back, flank or abdominal pain, often associated with kidney and/or ureter involvement
- Difficulty walking and balance (ataxia), slurred speech (dysarthria), uncoordinated limb movements (dysmetria) or eye movements (nystagmus)
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SIGNs
Depending on organ involvement, some of the following signs may be found.

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

Bilateral osteosclerosis of the long bones involving the diaphyseal 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/peri-orbital, 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.
**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

**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.

**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

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

**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.

- **EYES**
  - protruding eyes, vision problems (30%)
  - rash, yellow patches around eyes (25%)
  - cough and shortness of breath (50%)
  - growth around kidneys and reduced function, “hairy kidney” (50%)
  - Decreased hormones and fatigue (3%)

- **NERVOUS SYSTEM**
  - balance or swallowing issues, emotional swings (40%)

- **HORMONES**
  - extreme thirst and urination; extreme fatigue (50 – 70%)

- **ARTERIAL**
  - inflammation of blood vessels (50 – 80%)

- **HEART**
  - slowing of heart rate and shortness of breath (40 – 70%)

- **BONES**
  - bone pain (95%)

- **SUN**
  - increased uptake of the radionuclides in the distal tibia, less commonly in the axial skeleton.

- **TESTES**
  - bone pain

- **DIAGNOSIS**
  - baseline assessment.

- **MANAGEMENT**
  - treatment is recommended indefinitely as tolerated.

- **TREATMENTS**
  - BRAF-inhibitor vemurafenib for BRAF V600-mutation positive ECD
  - BRAF & MEK kinase inhibitors (cobimetinib, dabrafenib, and trametinib)

- **PATHOLOGY**
  - symptoms vary, depending upon the organ(s) involved.

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