



ECD GLOBAL ALLIANCE

Supporting those affected by
Erdheim-Chester Disease worldwide

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Endocrinology Guide for Erdheim-Chester Disease Care & Diagnosis

DEFINITION OF ERDHEIM-CHESTER DISEASE (ECD)

- A non-Langerhans cell histiocytic neoplasm that accumulates and infiltrates organs and tissues
- Multisystem disease affecting virtually any combination of organ systems, including ophthalmic/periorbital, pulmonary, cardiovascular, renal, musculoskeletal, dermatologic, endocrinologic, and central nervous systems
- Prompt diagnosis is critical for more favorable outcomes
- Usually diagnosed through biopsy, scans (bone, PET, MRI), and clinical symptoms

PROTEAN PRESENTATIONS

- Depends on organs involved
- Non-specific symptoms of bone pain, fevers, night sweats, weight loss, fatigue, and/or weakness are often present
- Findings may include:
 - HEENT: double vision, proptosis, retro-orbital pain
 - Cardiovascular: dyspnea, orthopnea, angina
 - Pulmonary: dyspnea, cough, obstructive sleep apnea
 - Musculoskeletal: bone pain
 - Dermatologic: xanthelasma, arcus senilis, rash
 - Endocrine: diabetes insipidus, growth hormone deficiency, hyperprolactinemia, panhypopituitarism, hypogonadism (primary > central in men), hypothyroidism (primary or central), adrenal insufficiency (central > primary), diabetes mellitus, dyslipidemia, obesity, infertility, osteoporosis
 - Neurologic: ataxia, dysarthria, dysphagia, cognitive decline
 - Psychiatric: depression, disinhibition, inappropriate laughing or crying
 - Nephrological: hairy kidney, renal failure, retroperitoneal fibrosis
- Typical onset between 40 and 70 years of age, although documented cases in all age groups
- Slight preponderance of males

BOARD OF DIRECTORS

The ECD Global Alliance is a 501 (C)(3) organization.

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TYPICAL RADIOLOGY FINDINGS

- Bilateral cortical sclerosis of the long bones involving the diaphyseal regions
- Strong bilateral long bone uptake of radioactive tracer on 99mTc bone scintigraphy or FDG-PET scans
- Encasing disease of organs - "hairy kidney," "coated aorta," retroperitoneal fibrosis, right atrial mass, pericarditis, sellar and suprasellar infiltrations, testicular infiltration

PATHOLOGY FINDINGS

Infiltration by foamy or lipid-laden, epithelioid or spindled histiocytes, with associated fibrosis, and/or inflammatory background; foam cell changes not always present

- ECD is a clonal proliferation of histiocytes that have a xanthogranuloma (XG) phenotype.
- Touton giant cells may be present
- Immunohistochemistry - ECD histiocytes are XG family phenotype:

CD68+	CD163+
Factor 13a+	S-100+/-
Fascin+	CD1a -
- *BRAF* V600E mutations in >50% of patients – can be tested by immunohistochemistry or by polymerase chain reaction (PCR) based assay
- Other MAPK pathway alterations, including kinase fusions, in <50% patients
- Foamy nature of histiocytes is a helpful clue, but is not required. ECD has a varied morphology including epithelioid and spindled histiocytes.
- Fibroinflammatory background of lymphocytes, plasma cells, neutrophils is often present – often misdiagnosed as a reactive process.

KEY POINTS FOR ENDOCRINOLOGISTS

- None of the pathologic changes are unique to ECD – clinical and radiographic features are key to diagnosis.
- High index of suspicion for ECD in patients with typical "hairy kidney," retroperitoneal, or bone involvement, especially if concomitant diabetes insipidus.
- Diabetes insipidus and/or hypogonadism may precede diagnosis of disease by several years
- Adrenal encasement/infiltration usually does not lead to primary adrenal insufficiency; central adrenal insufficiency is rare but must be considered
- All central and peripheral glands can be infiltrated, but hormonal perturbations are more frequent than visible morphological anomalies
- Hormonal deficits can appear years after diagnosis, consequently they must be re-evaluated on a yearly basis
- Men are at risk for infertility and should receive information about sperm conservation

- Metabolic syndrome in ECD is not well studied; obesity, dyslipidemia, hypertension and dysglycemia should be addressed
- Very important to pursue PET-CT scan from vertex to toe (whole body) to capture diametaphyseal involvement around knee joint and investigate for multi-organ involvement.
- ECD may coexist with Langerhans Cell Histiocytosis (LCH) or myeloid neoplasm.
- Molecular studies increasingly play a role in diagnosis and management.

TREATMENTS

FDA Approved Treatment

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

Options under clinical trials include:

- *BRAF* & MEK kinase inhibitors (cobimetinib, dabrafenib, and trametinib); monotherapy & combined treatments

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

- Immunotherapy (interferon)
- Chemotherapy (cladribine, clofarabine)
- Anti-inflammatory medications (anakinra, tocilizumab, infliximab)
- Immunosuppressants (sirolimus, methotrexate, mycophenolate mofetil, azathioprine)
- Steroids (e.g., prednisone)
- Surgical debulking

Physical/Occupational Therapy

BASELINE & MONITORING GUIDELINES

As a multisystem disease, a baseline evaluation, along with close monitoring are required for all patients. Monitoring is typically performed every 3 months until disease is stabilized and monitoring reduces to every 6 months.

Physical Evaluation

- HEENT: xanthelasma, exophthalmos, arcus senilis
- Cardiac: hypertension, irregular pulse, cardiomegaly, murmurs, ECG abnormalities
- Pulmonary: diminished aeration, rales
- Neurologic: disconjugate gaze, cranial nerve palsies, dysarthria, ataxic or magnetic gait, hyperreflexia
- Psychiatric: pseudobulbar affect
- Endocrine: small testicular size or infiltrated testicles, gynecomastia, erectile dysfunction, menstrual perturbations, hung reflexes, hair loss

*Radiological Evaluation

All patients:

- PET/CT including distal extremities (vertex-to-toes)
- MRI brain with contrast
- Cardiac MRI

Selected patients based on symptoms or organ involvement:

- CT sinuses with contrast
- CT chest, abdomen, and pelvis with contrast
- MRI sella turcica
- Technitium-99m bone scintigraphy
- MRI orbit with contrast
- MRI total spine with contrast
- Renal artery ultrasound
- High-resolution CT chest
- Pulmonary function tests
- Testicular ultrasound

*Laboratory Evaluation

- Complete blood count with differential
- Comprehensive metabolic panel including liver and kidney function assessments
- C-reactive protein
- Morning urine and serum osmolality
- Morning serum cortisol with ACTH
- FSH/LH with testosterone (males) and estradiol (females)
- TSH and free T4
- Prolactin and IGF-1
- *BRAF* V600 genotyping (in lesional tissue)
- Targeted-capture, next-generation sequencing of lesional tissue in *BRAF* V600-wild type cases for mutations in *ARAF*, *NRAS*, *KRAS*, *MAP2K1*, and *PIK3CA*.
- Fusion assay

*Goyal et al Blood 2020

Adrenal insufficiency sick day rules

- Subjects with adrenal insufficiency and ECD are at significant risk of morbidity and mortality if they have an adrenal crisis and require education on managing illness or stress, that is, steroid sick day rules.
- Clinicians are encouraged to rule out adrenal insufficiency periodically or when clinically indicated in every individual with ECD, and to educate on increasing the dose of steroids (double to triple) in individuals with adrenal insufficiency and ECD during illness (e.g. flu, fever).
- Additionally, every individual with AI and ECD should receive an emergency care plan that outlines the management of AI during crisis.

ECD REFERRAL CARE CENTERS

ECD Referral Care Centers are available to treat patients and/or provide consultation to local treating physicians when patients cannot travel. Find more information about these centers: <http://erdheim-chester.org/care-centers/>.

LEARN MORE

Contact an ECD-knowledgeable endocrinologist:

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