Histiocytic Neoplasms, Version 2.2021

Ronald S. Go, MD[1,*]; Eric Jacobsen, MD[2,*]; Robert Baiocchi, MD, PhD[3]; Ilia Buhtoiarov, MD[4,*]; Erin B. Butler, MD[5]; Patrick K. Campbell, MD, PhD[6]; Don W. Coulter, MD[7]; Eli Diamond, MD[8]; Aron Flagg, MD[9]; Aaron M. Goodman, MD[10]; Gaurav Goyal, MD[11]; Dita Gratzinger, MD, PhD[12]; Paul C. Hendrie, MD, PhD[13]; Meghan Higman, MD, PhD[14]; Michael D. Hogarty, MD[15]; Filip Janku, MD, PhD[16]; Reem Karmali, MD, MS[17]; David Morgan, MD[18]; Anne C. Raldow, MD, MPH[19]; Alexandra Stefanovic, MD[20]; Srinivas K. Tantravahi, MBBS, MRCP[21]; Kelly Walkovich, MD[22]; Ling Zhang, MD[23]; Mary Anne Bergman[24]; and Susan D. Darlow, PhD[24]

ABSTRACT

Histiocytic neoplasms are rare hematologic disorders accounting for less than 1% of cancers of the soft tissue and lymph nodes. Clinical presentation and prognosis of these disorders can be highly variable, leading to challenges for diagnosis and optimal management of these patients. Treatment often consists of systemic therapy, and recent studies support use of targeted therapies for patients with these disorders. Observation ("watch and wait") may be sufficient for select patients with mild disease. These NCCN Guidelines for Histiocytic Neoplasms include recommendations for diagnosis and treatment of adults with the most common histiocytic disorders: Langerhans cell histiocytosis, Erdheim-Chester disease, and Rosai-Dorfman disease.

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[1]Mayo Clinic Cancer Center; [2]Dana-Farber/Brigham and Women's Cancer Center |Massachusetts General Hospital Cancer Center; [3]The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute; [4]Case Comprehensive Cancer Center/University Hospitals Seidman Cancer Center and Cleveland Clinic Taussig Cancer Institute Cleveland Clinic Children's Hospital; [5]UT Southwestern Simmons Comprehensive Cancer Center; [6]St. Jude Children's Research Hospital/The University of Tennessee Health Science Center; [7]Fred & Pamela Buffett Cancer Center; [8]Memorial Sloan Kettering Cancer Center; [9]Yale Cancer Center/Smilow Cancer Hospital; [10]UC San Diego Moores Cancer Center; [11]O'Neal Comprehensive Cancer Center at UAB; [12]Stanford Cancer Institute; [13]Fred Hutchinson Cancer Research Center/ Seattle Cancer Care Alliance; [14]Roswell Park Comprehensive Cancer Center; [15]Abramson Cancer Center at the University of Pennsylvania; [16]The University of Texas MD Anderson Cancer Center; [17]Robert H. Lurie Comprehensive Cancer Center of Northwestern University; [18]Vanderbilt-Ingram Cancer Center; [19]UCLA Jonsson Comprehensive Cancer Center; [20]Duke Cancer Institute; [21]Huntsman Cancer Institute at the University of Utah; [22]University of Michigan Rogel Cancer Center; [23]Moffitt Cancer Center; and [24]National Comprehensive Cancer Network

[*]Discussion Writing Committee Member.

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The complete NCCN Guidelines for Histiocytic Neoplasms are not printed in this issue of JNCCN but can be accessed online at NCCN.org.

Disclosures for the NCCN Histiocytic Neoplasms Panel

At the beginning of each NCCN Guidelines Panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN Histiocytic Neoplasms Panel members can be found on page 1303. (The most recent version of these guidelines and accompanying disclosures are available at NCCN.org.)

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INTRODUCTION

These Guidelines describe treatment recommendations for adults with histiocytic neoplasms. In scenarios where there is little evidence in the adult population, recommendations are extrapolated from pediatric studies.

Overview

Histiocytic neoplasms represent hematologic disorders characterized by the accumulation of myeloid-dendritic cell-derived neoplastic cells with an accompanying inflammatory infiltrate.[1,2] They are rare, accounting for less than 1% of cancers of the soft tissue and lymph nodes.[2] Histiocytic neoplasms are heterogeneous, and presentation varies from localized and mild to disseminated and lethal.[1] Initial presentation is often nonspecific, which can lead to a significant delay in the diagnosis and treatment of histiocytic disorders,[3] and these patients should ideally be evaluated and treated at centers of expertise.

There are over 100 subtypes of histiocytoses.[1] The original classification of histiocytic neoplasms by the Working Group of the Histiocyte Society, which was published in 1987, categorized these disorders as follows: Langerhans cell, non-Langerhans cell, and malignant histiocytoses.[4] However, the categorization of histiocytic neoplasms as Langerhans/non-Langerhans may not be appropriate, because neoplasms classified as Langerhans cell histiocytosis (LCH) were discovered to share many of the same molecular features as those classified as Erdheim-Chester disease (ECD), following emerging deep sequencing diagnostic methods.[1,2] For example, clonal mutations of genes in the MAPK pathway have been found in the majority of Langerhans and non-Langerhans histiocytoses.[5–8] In 2016, the Histiocyte Society published a revised classification based on clinical, radiographic, histologic, phenotypic, and other molecular features, further dividing them into 5 groups of diseases: (1) Langerhans-related; (2) cutaneous and mucocutaneous; (3) malignant histiocytoses; (4) Rosai-Dorfman disease (RDD); and (5) hemophagocytic lymphohistiocytosis and macrophage activation syndrome.[1]

The NCCN Guidelines for Histiocytic Neoplasms include recommendations for diagnosis and treatment of adults with LCH, ECD, and RDD (though the WHO does not yet officially recognize RDD as a neoplasm). The evidence supporting the management of histiocytic neoplasms in adults is largely based on small retrospective studies, case series, and case reports, due to the paucity of prospective studies in adults. In addition, some of the diagnostic and treatment recommendations for adults with histiocytic neoplasms are, of necessity, extrapolated from prospective studies in children and young adults, except when stated otherwise.

Langerhans Cell Histiocytosis

WORKUP / EVALUATION[a]

Common Sites of Involvement:

- Bone
- Skin
- Lymph node
- Liver
- Spleen
- Oral mucosa
- Lung
- CNS

Medical History and Physical Examination

- Constitutional: Fevers, night sweats, fatigue, headache, myalgias
- HEENT: Double vision, blurry vision, decreased hearing, mass, lymphadenopathy
- Cardiovascular: dyspnea, orthopnea
- Pulmonary: dyspnea, cough, hemoptysis, chest pain, crackles, pneumothorax; evaluate smoking history[b]
- Musculoskeletal: bone pain, back pain
- Lymphatic: Lymphadenopathy
- Gastrointestinal: diarrhea, melena
- Skin: erythematous rash, subcutaneous nodules, attention to ear canals, infraorbital region, perineum, axillae, inguinal region, xanthelasma
- Endocrine: polydipsia/polyuria, decreased libido
- Neurologic: ataxia, dysarthria, seizures, cognitive decline, disconjugate gaze, cranial nerve palsies, dysarthria, ataxic or magnetic gait
- Psychiatric: Depression, anxiety

Radiologic Evaluation

- Whole-body PET/CT[c] including distal extremities (vertex to toes)
- High-resolution CT of the chest for pulmonary LCH

Selected Patients Based on Symptoms or Organ Involvement

- MRI brain/mastoid/pituitary with contrast
- MRI sella turcica
- Right heart catheterization
- Trans-thoracic echocardiogram
- Pulmonary function tests
- CT chest, abdomen, and pelvis with contrast
- US abdomen (liver/spleen)
- Endoscopic retrograde cholangiopancreatography (ERCP) (if LFTs abnormal or ducts dilated on CT/US)
- Panorex x-ray

Laboratory Evaluation

- Complete blood count (CBC) with differential (see LCH-2)
- 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
- Tissue biopsy[d] (see LCH-2)
  - *BRAF* V600E (VE1) immunohistochemistry
  - Targeted-capture, next-generation sequencing (NGS) in *BRAF* V600 E wild-type or equivocal cases for mutations in the MAPK pathway such as *ARAF, NRAS, KRAS, MAP2K1,* and *PIK3CA*
  - Gene fusion assay
- Bone marrow aspirate/biopsy (see LCH-2)

Subspecialty Consultations as Needed

- Pulmonary
- Neurology
- Endocrinology
- Dermatology prior to initiation of BRAF or MEK inhibitor therapy[e]
- Ophthalmology prior to initiation of MEK inhibitor therapy[e]
- Dental/Periodontal
- Smoking cessation[b]
- Palliative medicine

See Treatment (LCH-3)

[a]Adapted with permission from Goyal G, et al. Mayo Clin Proc 2019;94:2054-2071.
[b]Provide resources for smoking cessation. See NCCN Guidelines for Smoking Cessation†.
[c]For patients with high-risk bone lesions and/or suspected to have multisystem disease.
[d]See Principles of Pathology (HIST-A).
[e]See Management of Toxicities Associated with Targeted Therapy (ME-K) in the NCCN Guidelines for Melanoma: Cutaneous.†

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Pathologic Analysis of Histiocytic Neoplasms

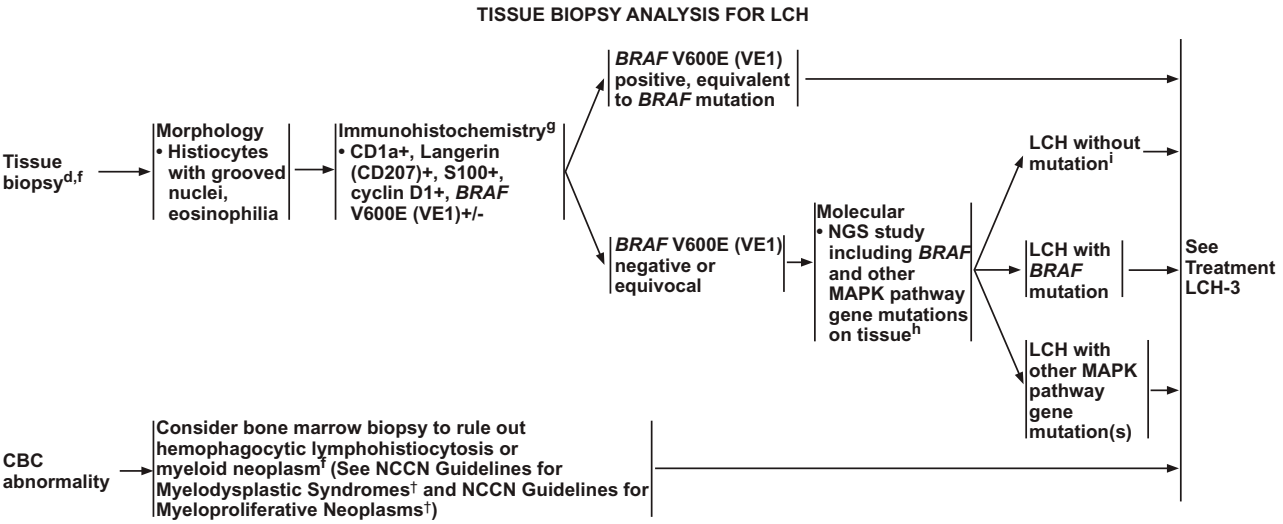
Immunohistochemical (IHC) analysis plays an important role in the diagnosis and should be performed when a histiocytic neoplasm is suspected. The basic IHC panel should include CD163/CD68, S100, CD1a, langerin/CD207, cyclin D1, and factor XIIIa as indicated.[3] *BRAF* V600E (VE1) IHC is recommended for LCH and ECD. Anaplastic lymphoma kinase (ALK) may also be included as clinically indicated to identify *ALK*-rearranged histiocytoses.[9] IHC analysis can be helpful in the broad differential diagnosis of histiocytosis, including varied entities such as composite IgG4-related disease and B-cell lymphoma, as well as infection, fat necrosis, and idiopathic retroperitoneal fibrosis.[3]

Next-generation sequencing (NGS) of tumor tissue for identification of mutations in the RAS/RAF/MAPK/ERK and PI3K/AKT pathway genes can be instrumental in the diagnosis of histiocytic neoplasms and can also inform systemic therapy decision-making.[3] Additionally, fusion testing should include *BRAF, ALK,* and *NTRK1* rearrangements. A complete list of fusions and rearrangements to include in the evaluation can be found in the "Summary of Pathologic and Molecular Features of Histiocytic Neoplasms" in the algorithm (HIST-A; page 1290). If fusion panel testing is unavailable, then IHC or fluorescence in situ hybridization may be used to evaluate for *ALK* rearrangements. Molecular testing can be done either in a stepwise fashion or in parallel, depending on clinical indication and institutional protocols. If a specific histiocytic disorder is suspected, then stepwise testing should be tailored based on the mutations known to be associated with that disorder. FDG-PET/CT may be useful for determining the extent of the disease and for guiding biopsies. Details regarding recommendations for pathologic analysis related to LCH, ECD, and RDD are detailed in subsequent sections and in the algorithm (HIST-A; page 1290).

Langerhans Cell Histiocytosis

LCH is the most common histiocytic disorder. It is more common in children than adults, with 5 to 9 cases per 1 million in children (>15 years) and 1 case per 1 million in adults (>15 years).[10,11] Though many cases are mild and asymptomatic, rapidly progressing and/or disseminated

Langerhans Cell Histiocytosis



Immunophenotype key: +/-: positive or negative; +: positive; –: negative

[d]See Principles of Pathology (HIST-A).
[f]For patients with suspected LCH or histiocytosis and biopsy is not possible because of location or risk factors, mutational analysis of the peripheral blood is an option.
[g]A minimal panel would include CD1a, S100, and Langerin; cyclin D1 and *BRAF* V600E (VE1) immunohistochemistry is recommended.
[h]Fresh or paraffin-embedded tissue is used for NGS study; peripheral blood may be informative in multisystem disease. The NGS panel should cover the common MAPK pathway mutations (*BRAF, ARAF, NRAS, KRAS, MAP2K1,* and *PIK3CA*).
[i]Molecular testing for somatic mutations and fusions can be performed in a stepwise manner or in parallel, depending on clinical need and institutional protocols. The frequency of suspected molecular lesions should drive the order of testing if a stepwise algorithm is chosen. Allele-specific polymerase chain reaction (PCR) for *BRAF* V600E mutations can be the first step if *BRAF* V600E (VE1) immunohistochemistry is not available or is equivocal. Somatic mutation NGS panel testing should cover the common MAPK pathway mutations. RNA-based molecular panel including fusion testing should cover *BRAF*, *ALK*, and *NTRK1* rearrangements. If there is clinical concern for *ALK* rearrangement, or if fusion panel testing is not available, ALK immunohistochemistry and fluorescence in situ hybridization (FISH) studies may be performed.

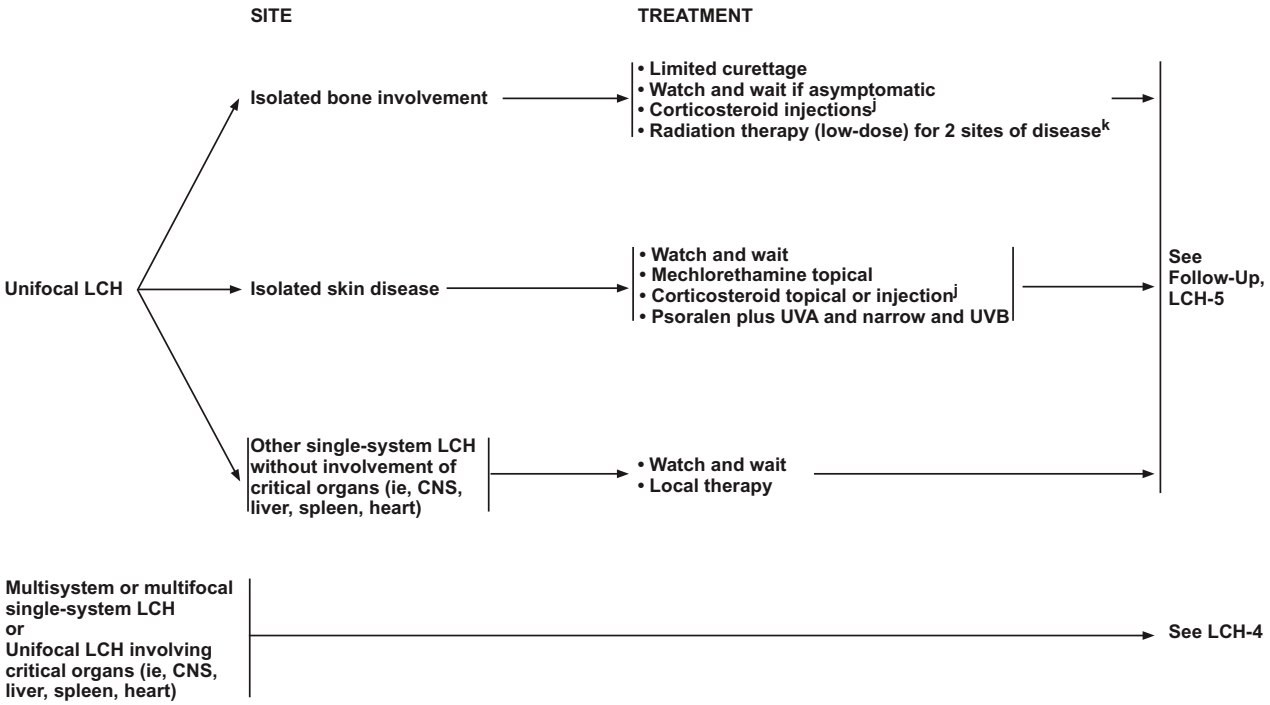
[†]To view the most recent version of these guidelines, visit NCCN.org.

life-threatening disease that is resistant to treatment may also occur. Common sites of involvement of LCH include bone, skin, pituitary gland, liver, spleen, bone marrow, lungs, and lymph nodes.[12] A pulmonary form of LCH can occur in adults and is associated with smoking.[13–15] Multifocal bone lesions without the involvement of other organs may also be observed in some cases, and bone mineral density may be lower than the expected range in adults with LCH.[16] Permanent endocrinopathy is common in LCH, such as diabetes insipidus, which more commonly occurs with multisystem disease.[14,17,18] Though there are cases of solitary central nervous system (CNS)-involved LCH, CNS involvement is most often accompanied with multisystem disease.[12] There is a high prevalence of concomitant and subsequent malignancies, especially solid tumors or myeloid malignancies, in adults with LCH.[19,20]

CNS-involved LCH can present as space-occupying granulomatous tumors, frequently in the hypothalamic-pituitary region but also involving the choroid plexus, meninges, gray or white matter, or as neurodegenerative LCH (ND-LCH) lesions in the cerebellum and brain stem.[21] The bone lesions in the mastoid, sphenoid, orbit, temporal bone, and clivus represent CNS-risk lesions, indicating increased risk of developing CNS LCH.[21] ND-LCH is frequent in patients with pituitary, skin, and base-of-skull bone involvement. A study of children and young adults with LCH (n=1,897) showed that a *BRAF* mutation was present in 93.7% of patients with ND-LCH, compared with 54.1% in patients without ND-LCH.[22] The 10-year risk of developing neurodegenerative disease is 33.1% in patients with a *BRAF* mutation, compared with 2.9% in patients without a *BRAF* mutation (*P*=.002).

The Histiocyte Society's initial 1987 classification categorized LCH as an immunologic inflammatory disease but not as a neoplasm.[4] However, presence of clonal histiocytes supports the neoplastic origin of LCH.[14,23] Recurrent activating mutations in the MAPK pathway are found in the vast majority of cases.[8,24] These discoveries support the WHO's classification of histiocytic disorders, particularly LCH as a neoplastic process.[25] In the Histiocyte Society's revised clas-

Langerhans Cell Histiocytosis



[j]Triamcinolone injection or equivalent corticosteroid.
[k]Use clinical judgment for 3 sites.

LCH-3

sification, 4 categories of LCH are identified: single system, pulmonary-involved, multisystem with risk organ involvement, and multisystem without risk organ involvement.[1]

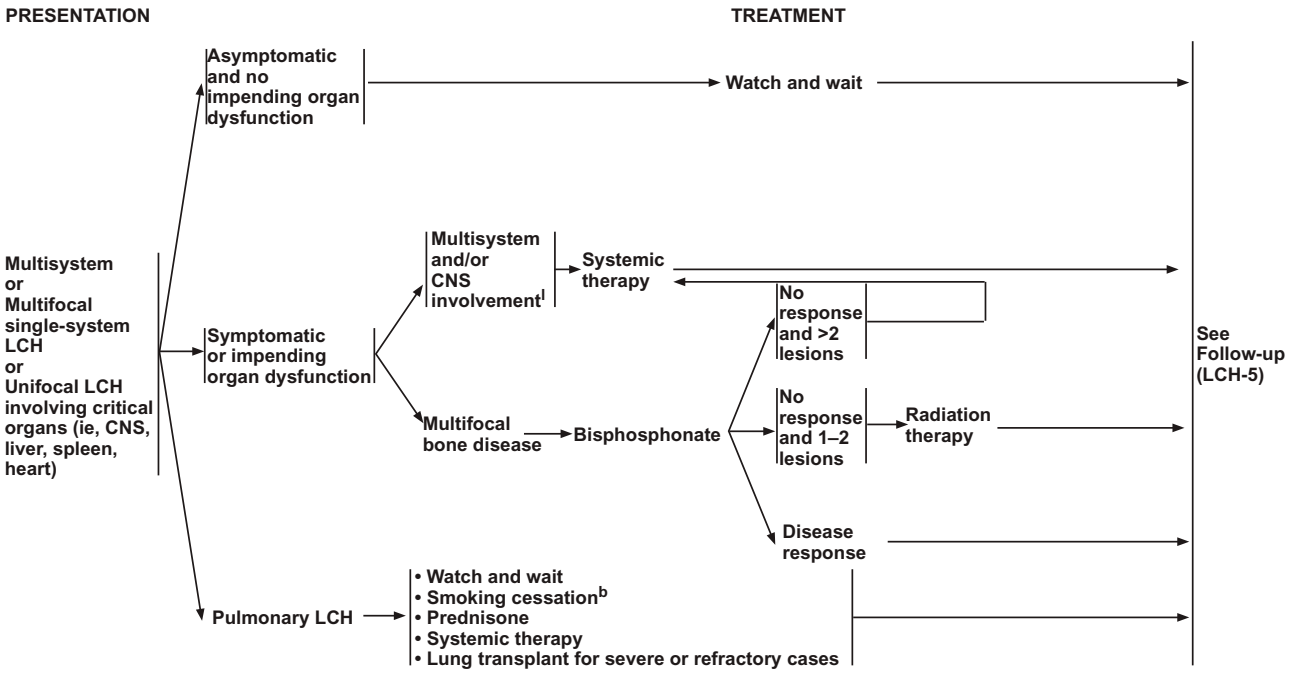
Diagnosis of LCH

Diagnosis of LCH is based on clinical and radiologic findings, though biopsy of tumor tissue is also recommended (see "Histopathologic Characterization of LCH," page 1283).[14] Initial diagnostic testing is dependent on clinical presentation. A detailed review of symptoms and comprehensive physical examination of the skin; head, eyes, ears, nose, and throat (HEENT); and cardiovascular, pulmonary, musculoskeletal, lymphatic, gastrointestinal, endocrine, and neurologic systems should be performed.[14] Comprehensive neurocognitive and psychological assessments are also recommended in select patients.[14]

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.[26–28] Bone involvement, which may appear as aggressive cortically based lytic lesions, is best detected using full-body (vertex-to-toes) FDG-PET/CT.[3] It is controversial whether whole-body imaging is required for every patient with LCH, such as those presenting only with skin involvement, or those with symptoms limited to the lungs. However, whether a patient's LCH is single or multisystem is unknown in the absence of staging. Therefore, whole-body PET/CT should be considered for patients with suspected multisystem disease.

Abnormal brain MRI is often observed in LCH, even in the absence of neurologic symptoms.[12] Findings on brain MRI can mimic primary CNS tumors, brain metastases, or inflammatory granulomatous diseases.[12] In ND-LCH, signal changes in white and deep gray matter with cortical atrophy may be observed with MRI.[21] In cases that manifest with diabetes insipidus, the earliest change seen on MRI may be an enlargement of the pituitary stalk, and later the space-occupying tumors extending to the pituitary gland and hypothalamus. There is typically a "loss of bright spot" (ie, the lack of the physiologic hyperintense signal in the posterior pituitary on T1-weighted images), which is secondary to the loss

Langerhans Cell Histiocytosis



[b]Provide resources for smoking cessation. See NCCN Guidelines for Smoking Cessation†.
[l]For neurodegenerative LCH, imaging changes precede clinical progression. Cognitive symptoms should be carefully monitored, and early treatment considered.

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of antidiuretic hormone-containing granules. Not all patients with diabetes insipidus will have an abnormal MRI.

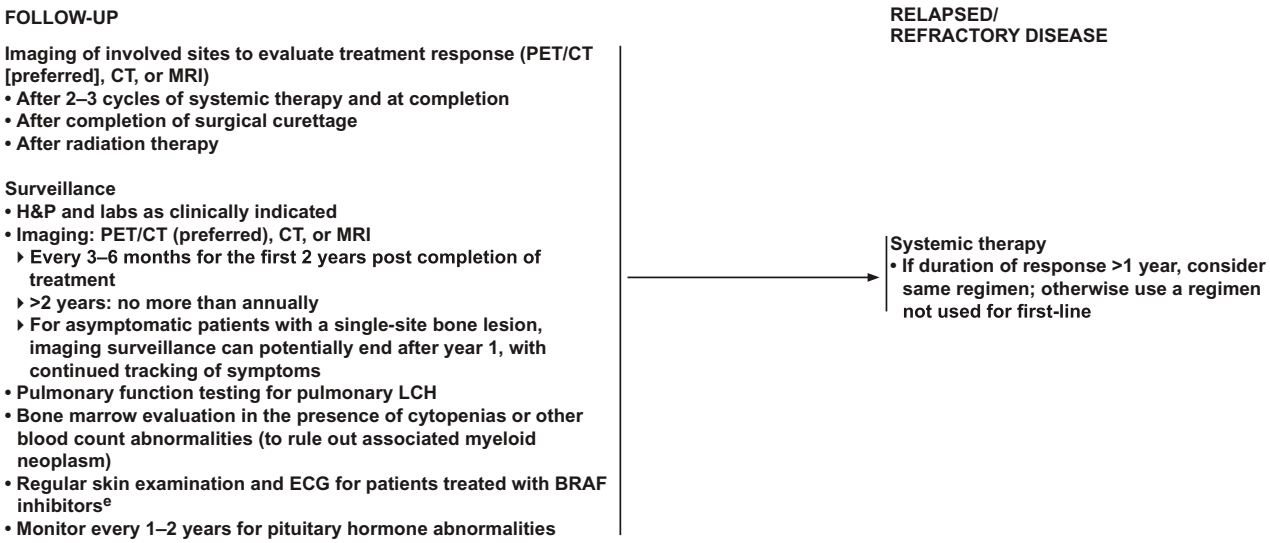
Ultrasound of the abdomen and neck can discover hepatic and thyroid involvement, respectively.[14] However, ultrasound is probably not needed if a PET has been performed. Other imaging techniques (eg, endoscopic retrograde cholangiopancreatography; CT of chest, abdomen, and pelvis; and panorex X-ray) may be performed as clinically indicated.

High-resolution chest CT may detect nodules 2 mm or less in the early stages of pulmonary LCH, and irregular cysts in the lungs may be observed in advanced disease.[3,14] Pulmonary function testing should be considered to evaluate obstructive airway disease, air trapping, and carbon monoxide diffusing capacity.[13,14] Echocardiogram is also recommended to screen for pulmonary hypertension.[3]

Laboratory tests should include complete blood count (CBC), blood chemistry, coagulation studies, thyroid-stimulating hormone, free T4, urine analysis, C-reactive protein, and morning serum cortisol with adrenocorticotropic hormone.[14] Prolactin and insulin-like growth factor-1 level should be considered in select patients, as well as 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. Biopsy of tumor tissue is recommended in all cases. *BRAF* V600E (VE1) IHC is recommended on all tissue biopsy samples, and NGS of tumor tissue for somatic variants in the MAPK pathway genes, as well gene fusion assay, is recommended in patients with *BRAF* V600E wild-type or equivocal disease. NGS of the peripheral blood is an alternative if biopsy is not feasible due to tumor location or other reasons (see "Pathologic Analysis of Histiocytic Neoplasms" [page 1279] and "Histopathologic Characterization of LCH" [page 1283]).

Because LCH frequently presents with lytic bone lesions, differential diagnosis may include multiple myeloma and metastatic bone involvement from other cancers. Skin involvement may be mistaken for seborrheic dermatitis, eczema, psoriasis, Candida infection, intertrigo, and lichen planus.[14] Langerhans cell hyperplasia

Langerhans Cell Histiocytosis



[e]See Management of Toxicities Associated with Targeted Therapy (ME-K) in the NCCN Guidelines for Melanoma: Cutaneous[†].

[†]To view the most recent version of these guidelines, visit NCCN.org.

can be associated with mycosis fungoides, which could be misinterpreted as a composite LCH.[29] Differential diagnosis for single-system pulmonary LCH includes hypersensitivity pneumonitis, interstitial pneumonia, pulmonary lymphangioleiomyomatosis, and sarcoidosis.

The complete recommendations for evaluation of LCH are provided in the algorithm and are adapted from recommendations in the consensus statement by the Mayo Clinic Histiocytosis Working Group[3] (see "Langerhans Cell Histiocytosis: Workup/Evaluation" in the algorithm, page 1279 [LCH-1]). Subspecialty consultations (eg, pulmonary and smoking cessation, neurology, endocrinology) should be carried out as clinically indicated. Dermatology consultation is recommended for patients treated with certain targeted therapies (ie, BRAF and MEK inhibitors) for diagnosis and treatment of skin-related toxicities.[30] Retinal evaluation may be considered due to the high incidence of serous retinopathy with MEK inhibitors.[31,32]

Histopathologic Characterization of LCH

LCH tumors often demonstrate neoplastic histiocytes admixed with marked inflammatory cell infiltration. On hematoxylin and eosin (H&E) stain, neoplastic LCH cells are mononucleated, typically with a coffee bean-shaped nucleus.[1,24,33] Abundant eosinophils and multinucleated giant cells are frequently observed.[1–3] Fibrosis may be present, particularly in bone lesions.[3] IHC analysis of the LCH tumors shows abundant CD1a- and CD207- (langerin) positive neoplastic histiocytes and can also be positive for S100.[3,24,33] Pathology of lesions from LCH-associated abnormal CNS imaging and LCH-associated abnormal CNS symptoms show infiltrating CD8+ lymphocytes, and, unlike other LCH tumors, lack CD1a-positive histiocytes.[34] Cyclin D1 can be helpful for differentiating neoplastic Langerhans cells from reactive Langerhans cell proliferation.[35,36] Birbeck granules can be identified by electron microscope, which is, however, now not commonly performed.

Activation of RAS-RAF-MAPK pathway is universal in all patients with LCH.[5,37] *BRAF* V600E activating mutation is present in 38% to 64% of LCH cases,[5,6,38–42] and this mutation is more frequent in mixed LCH/ECD, when compared with isolated LCH or ECD.[43] Mutations in *MAP2K1* are also prevalent in LCH (~20%).[8,38,42,44] *BRAF*

Erdheim-Chester Disease

WORKUP / EVALUATION[a]

Common Sites of Involvement
- Long bones in most cases
  - Bilateral and symmetric diaphyseal and metaphyseal osteosclerosis with subchondral sparing
- Other sites include:
  - Orbits: retro-orbital mass with exophthalmos; xanthelasma
  - CNS: pituitary gland, posterior fossa
  - Lungs - interstitial changes
  - Vascular: periaortic infiltrate; pericardium, right atrium
  - Retroperitoneal/perinephric ("hairy kidney"); mesentery

Medical History and Physical Examination
- Constitutional: Fevers, night sweats, fatigue
- HEENT: double vision, retro-orbital pain, xanthelasma, exophthalmos
- Cardiovascular: dyspnea, orthopnea, hypertension, irregular pulse, bradycardia, cardiomegaly, murmurs
- Pulmonary: dyspnea, cough, diminished aeration, rales
- Neurologic: disconjugate gaze, cranial nerve palsies, dysarthria, ataxic or magnetic gait, sensory or motor impairment, hyperreflexia, ataxia, dysarthria, dysphagia, limb weakness, cognitive decline
- Musculoskeletal: bone pain
- Dermatologic: xanthelasma, rash
- Endocrine: polydipsia/polyuria, gynecomastia, decreased libido
- Psychiatric: depression, anxiety, disinhibition, inappropriate laughing or crying, pseudobulbar affect

Radiologic Evaluation
- Whole-body 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
- Trans-thoracic echocardiogram
- MRI sella turcica
- Technetium-99^{m} MDP 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
- CBC with differential (see ECD-2)
- 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
- Tissue biopsy[b] (see ECD-2)
  - *BRAF* V600E (VE1) immunohistochemistry
  - Targeted-capture, NGS in *BRAF* V600E wild-type or equivocal cases for mutations in the MAPK pathway such as *ARAF, NRAS, KRAS, MAP2K1,* and *PIK3CA*
  - Gene fusion assay
- Bone marrow aspirate/biopsy (see ECD-2)

Subspecialty Consultations as Needed
- Neurology
- Endocrinology
- Nephrology
- Urology
- Dermatology prior to initiation of BRAF or MEK inhibitor therapy[c]
- Ophthalmology prior to initiation of MEK inhibitor therapy[c]

See Treatment (ECD-3)

[a]Adapted with permission from Goyal G, et al. Blood 2020;135:1929-1945.
[b]See Principles of Pathology (HIST-A).
[c]See Management of Toxicities Associated with Targeted Therapy (ME-K) in the NCCN Guidelines for Melanoma: Cutaneous†.

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V600E and *MAP2K1* mutations are mutually exclusive in LCH.[44] *KRAS, NRAS, ARAF,* and *CSF1R* mutations are less frequently observed in LCH.[45,46]

BRAF V600E (VE1) should be evaluated using IHC. However, studies evaluating IHC versus PCR testing of *BRAF* V600E mutations in pediatric patients with LCH (using stringent scoring criteria[47]) showed sensitivity values ranging from 35.6% to 80%; specificity values ranged from 75.5% to 100%.[48,49] *BRAF* V600E allele-specific PCR is recommended if IHC is unavailable or when *BRAF* V600E (VE1) IHC results are equivocal or negative. 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.

For complete recommendations regarding pathologic analysis of LCH cases, see the "Principles of Pathology" in the algorithm (HIST-A; page 1290).

Treatment of LCH

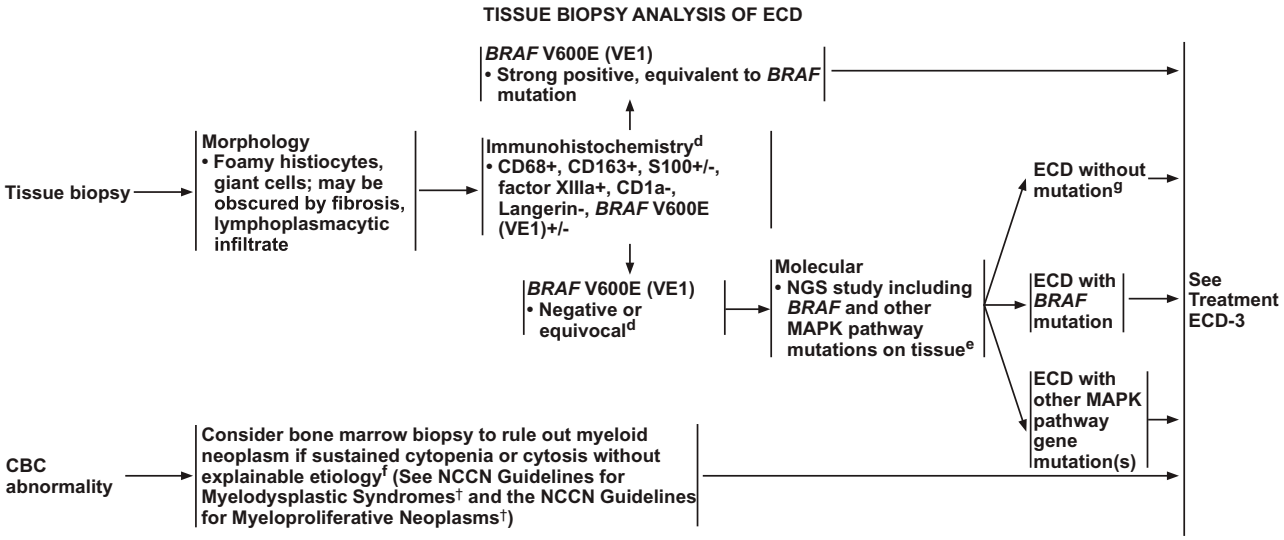
Much of the evidence for treatment of LCH is extrapolated from prospective studies of children and adolescents. Studies of adults with LCH are limited to case series and retrospective studies. Treatment decisions of LCH should be made based on sites and extent of disease.[14]

Unifocal and Single System Disease With No Critical Organ Involvement

For patients with single system disease and no involvement of critical organs (ie, CNS, liver spleen, heart), treatment is limited to local therapy and observation (watch and wait).[14]

Limited curettage is recommended for patients with isolated bone lesions,[50] but complete resection of bone lesions is not recommended, as this may result in an increase in the size of the bony defect and permanent skeletal defects.[14] Steroid injection may facilitate healing after limited curettage.[14] Radiation therapy for treatment of bone-involved LCH is associated with excellent local disease control.[51,52] For patients with single system bone disease, radiation therapy may be used for some patients with limited sites of disease, specifically in cases with impending neurologic dysfunction and if surgical risk is

Erdheim-Chester Disease



Immunophenotype key: +/-: positive or negative; +: positive; –: negative

[d]A minimal panel would include CD68 or CD163, factor XIIIa, S100, CD1a; *BRAF* V600E (VE1) immunohistochemistry is recommended.

[e]Fresh or paraffin-embedded tissue is used for NGS study; peripheral blood testing may be informative in multisystem disease. The NGS panel should cover the common MAPK pathway mutations (*BRAF, ARAF, NRAS, KRAS, MAP2K1,* and *PIK3CA*). If clinically indicated in cases without the usual MAPK pathway mutations, FISH for *BRAF*, *ALK*, or *NTRK1* fusions may be performed.

[f]For patients with suspected ECD or histiocytosis and biopsy is not possible because of location or risk factors, mutational analysis of the peripheral blood is an option. Janku F, et al. Mol Cancer Ther. 2019;18:1149-1157.

[g]Molecular testing for somatic mutations and fusions can be performed in a stepwise manner or in parallel, depending on clinical need and institutional protocols. The frequency of suspected molecular lesions should drive the order of testing if a stepwise algorithm is chosen. Allele-specific PCR for *BRAF* V600E mutations can be the first step if *BRAF* V600E (VE1) immunohistochemistry is not available or is equivocal. Somatic mutation NGS panel testing should cover the common MAPK pathway mutations. RNA-based molecular panel including fusion testing should cover *BRAF*, *ALK*, and *NTRK1* rearrangements. If there is clinical concern for *ALK* rearrangement, or if fusion panel testing is not available, ALK immunohistochemistry and FISH studies may be performed.

†To view the most recent version of these guidelines, visit NCCN.org.

ECD-2

high.[14] "Limited" sites of disease is generally defined as 1 to 2 lesions in this context, though radiation therapy may be considered for up to 3 bone lesions as clinically indicated. The recommended radiation dose for treatment of bone-involved LCH in adults is 10 to 20 Gy.[14,51] Watch and wait is also reasonable for asymptomatic and isolated bone lesions.

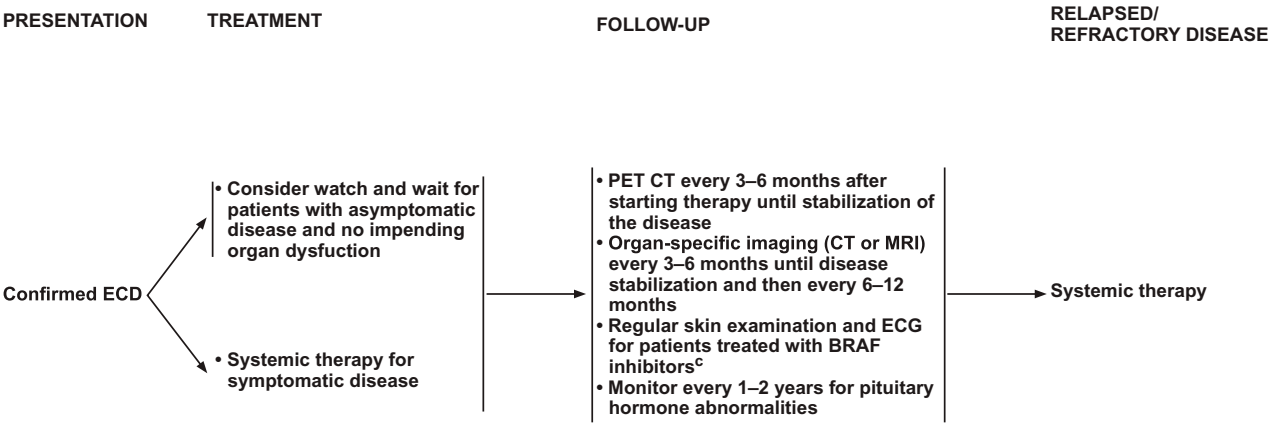
For patients with single system isolated skin disease, topical therapies may be used.[50] Case reports describing treatment of older adults with cutaneous LCH support the use of psoralen with ultraviolet A and narrow band ultraviolet B.[53,54] Other topical therapies such as nitrogen mustard (eg, mechlorethamine) and steroids are alternative options that have been shown to be effective in children with cutaneous LCH,[55,56] though there are no published data in adults with LCH. Surgery should only be done for solitary skin lesions, and only for those in which surgery will not result in disfigurement. Systemic therapy may be used for symptomatic disease including pain, secondary infection, or if there are complications from skin lesions.[50] Isolated skin-involved LCH has been reported to resolve spontaneously,[57] so watch and wait is also an option for these patients.

Multifocal or Multisystem Disease or Unifocal Disease With Critical Organ Involvement

Systemic therapy is often required for the treatment of multisystem LCH, multifocal single system, or unifocal but involving a critical organ such as CNS, liver, spleen, or heart (see "Systemic Therapy," subsequent section). However, if asymptomatic or if there is no impending organ dysfunction, watch and wait may be considered. Imaging changes precede clinical progression in ND-LCH, warranting consideration of early treatment.

Because pulmonary LCH is associated with smoking, treatment should include smoking cessation (see the NCCN Guidelines for Smoking Cessation, available at NCCN.org). Pulmonary LCH could resolve with smoking cessation alone.[50] Therefore, watch and wait is an option, particularly in patients with asymptomatic disease or who have minor symptoms. Systemic therapy can be considered in patients with symptomatic and/or progressive pulmonary LCH, as well as in patients with

Erdheim-Chester Disease



[c]See Management of Toxicities Associated with Targeted Therapy (ME-K) in the NCCN Guidelines for Melanoma: Cutaneous[†].

[†]To view the most recent version of these guidelines, visit NCCN.org.

persistent disease despite smoking cessation (see "Systemic Therapy," next section). High-dose prednisone (1 mg/kg/day for 1 month, followed by a slow taper) can also be effective in treatment of pulmonary LCH.[14] Steroid treatment is often associated with radiographic improvements in pulmonary LCH but may not improve the respiratory function.[58] Lung transplant should be considered only in select patients with highly refractory and severe disease.[50]

Bisphosphonates (eg, zoledronic acid or pamidronate) for treatment of multifocal bone disease is supported by small retrospective studies and case series.[59,60] In the absence of disease response after treatment with a bisphosphonate, other systemic therapy regimens may be considered (see "Systemic Therapy," next section). Radiation therapy can also be considered in patients with persistent disease with limited disease sites after systemic treatment.[14] Systemic treatment with indomethacin was reported as a successful alternative therapeutic approach for some patients with primary and recurrent bone LCH.[61]

Systemic Therapy

Systemic therapy is the standard treatment for multisystem and/or multifocal LCH, but responses to commonly used regimens in adults with LCH tend to be less robust compared with children.[14] Evidence supporting use of chemotherapy in adults with LCH is based on small nonrandomized studies. Vinblastine and prednisone is the preferred chemotherapy-based treatment for LCH in the pediatric setting.[24] In a retrospective study conducted at a single center including 58 adults with bone-involved LCH, use of vinblastine and prednisone was associated with worse outcomes. In this study, 84% of patients who received vinblastine and prednisone developed progressive disease within the first year, compared with 21% of patients who received cytarabine (odds ratio [OR], 20.3; 95% CI, 4.20–98.20; $P<.001$).[62] For patients who received cladribine, 59% did not respond to treatment or relapsed in the first year. Cytarabine was the least toxic of the 3 regimens, with grade 3 to 4 adverse events being reported in 20% of patients who received cytarabine, compared with 37% and 75% who received cladribine and vinblastine/

Rosai-Dorfman Disease

WORKUP / EVALUATION[a]

Common Sites of Involvement
- Peripheral lymphadenopathy
- Subcutaneous nodules
- Extranodal sites:
  - Skin
  - Soft tissue
  - Upper respiratory tract
  - Bone
  - Retroperitoneum
  - Orbits

Medical History and Physical Examination
- Constitutional: fevers, night sweats, fatigue
- HEENT: cervical lymphadenopathy, double vision, retro-orbital pain, eyelids/lacrimal swelling, proptosis, nasal obstruction, epistaxis, hyposmia, oral sores, or pain, dysmorphic facies, and hearing abnormalities (familial RDD), enlarged tongue or tonsils
- Cardiovascular: dyspnea, orthopnea, hypertension, irregular pulse, cardiomegaly, murmurs
- Pulmonary: dyspnea, cough
- Thoracic: diminished lung aeration, rales, axillary nodes, breast mass
- Abdominal/gastrointestinal: flank mass, hepatosplenomegaly, enlarged inguinal nodes, abdominal pain, constipation, hematochezia
- Genital: testicular mass or enlargement
- Renal: hematuria, flank pain
- Musculoskeletal: bone pain, osseous mass
- Skin: rash, pruritus, nodules, papules, or plaques
- Endocrine: polydipsia/polyuria
- Neurologic: headaches, seizures, gait difficulty, limb or facial weakness, sensory changes, hearing impairment, new or focal back pain, disconjugate gaze, cranial nerve palsies, dysarthria, ataxic gait, hemiparesis, hyperreflexia
- History of autoimmune disease, autoimmune lymphoproliferative syndrome (ALPS), malignancy, LCH, or another histiocytic disorder
- Family history: consanguineous parents, autoimmune disease, Turkish/Pakistani or Middle Eastern background

Radiologic Evaluation
- Whole-body PET/CT including distal extremities (vertex to toes)

Selected Patients Based on Symptoms or Organ Involvement
- CT sinuses with contrast
- CT of the chest, abdomen, and pelvis with contrast
- MRI orbit/brain with contrast
- MRI spine with contrast
- High-resolution CT chest
- Trans-thoracic echocardiogram
- Pulmonary function tests
- Thyroid ultrasound
- Testicular ultrasound

Laboratory Evaluation
- CBC with differential
- Serum immunoglobulins
- ALPS panel, antinuclear antigen (ANA), antineutrophil cytoplasmic antibodies (ANCA), rheumatoid factor (RF), HLA-B27: if autoimmune disease is suspected and based on clinical findings
- C-reactive protein
- Complete metabolic panel, coagulation parameters, uric acid, LDH
- Patients with anemia: Coombs test, haptoglobin, reticulocyte count, and blood smear
- Tissue biopsy[b] (See RDD-2)
  - Targeted-capture, NGS of lesional tissue for mutations in MAPK pathway (eg, KRAS, MAP2K1) (See RDD-2)
  - Gene fusion assay
- Bone marrow aspirate/biopsy (if cytopenias or abnormal peripheral blood smear are present)
- Lumbar puncture (for brain lesions inaccessible to biopsy)
- Germline mutations in *SLC29A3*: if familial RDD is suspected

Subspecialty Consultations as Needed
- Dermatology and ophthalmology prior to initiation of MEK inhibitor therapy[c]

[a]Adapted with permission from Abla O, et al. Blood 2018;131:2877-2890.
[b]See Principles of Pathology (HIST-A).
[c]See Management of Toxicities Associated with Targeted Therapy (ME-K) in the NCCN Guidelines for Melanoma: Cutaneous†.

†To view the most recent version of these guidelines, visit NCCN.org.

See Treatment (RDD-3)

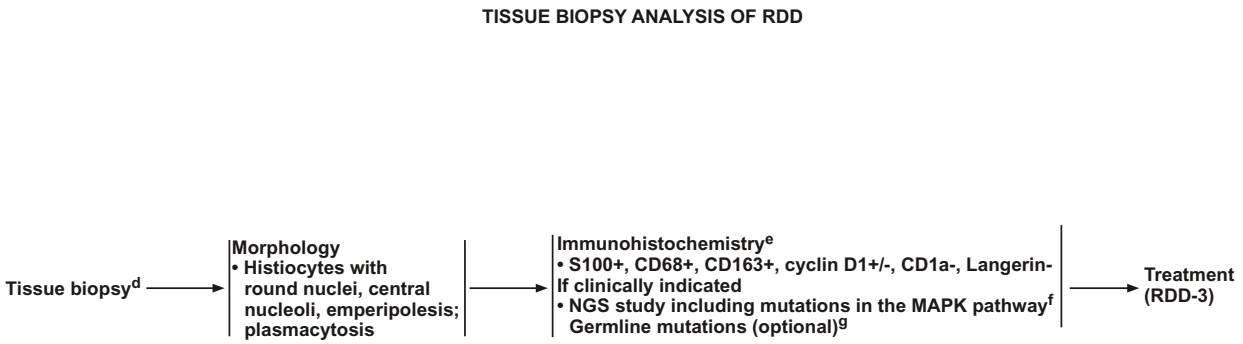
prednisone, respectively. Low-dose cytarabine is better tolerated in adults, but higher doses should be used for patients with CNS lesions.

Cladribine is another chemotherapy option that has been shown to be active in adults with LCH (overall response rate [ORR], 75%), based on results from a small phase II trial.[63] A more recent retrospective study conducted at an NCCN Member Institution also showed a high ORR (79%) in adults with multifocal LCH (n=38; 82% multisystem) who were treated with cladribine, with complete response (CR) and partial response (PR) observed in 26% and 53% of patients, respectively.[64] Five-year overall survival (OS), progression-free survival (PFS), and duration of response (DOR) for the sample was 75%, 58%, and 70%, respectively. There is also evidence supporting clofarabine for relapsed/refractory LCH in the pediatric setting, with disease improvement observed in 73% of 11 patients.[65] Neutropenia occurred in all patients.

A prospective single-center phase II trial from China examined combination of cytarabine (100 mg/m^2) and methotrexate (1 g/m^2) as treatment of adults with multisystem or single system multifocal LCH (n=83). ORR, 3-year OS, and 3-year event-free survival were 87.9%, 97.7%, and 68.0%, respectively.[66] A retrospective study conducted at a hospital in China examined cytarabine and methotrexate combination in adults with multisystem pulmonary-involved LCH (n=29). Pulmonary function was stable in 72.4% (n=24), improved in 13.8% (n=4), and deteriorated in 13.8% (n=4) of patients.[67] Since both cytarabine and methotrexate cross the blood-brain barrier, this combination regimen may be ideal for treatment of CNS-involved LCH.[66] High-dose methotrexate is also an option for CNS-involved LCH, based on a case report of a patient with CNS-involved ECD.[68] In addition, cytarabine in combination with intravenous immunoglobulin or vincristine demonstrated therapeutic potential in children and young adults with CNS-LCH and ND-LCH.[69,70]

Multifocal skin disease may respond to systemic therapy treatment for multisystem LCH in general.[14] However, small retrospective studies and case reports

Rosai-Dorfman Disease



Immunophenotype key: +/-: positive or negative; +: positive; –: negative

[d]For patients with suspected RDD or histiocytosis and biopsy is not possible because of location or risk factors, liquid biopsy for mutational analysis in the peripheral blood is an option. Janku F, et al. Mol Cancer Ther. 2019;18:1149-1157.

[e]A minimal panel would include CD68 or CD163, S100, CD1a, and cyclin D1. Of caution, cyclin D1 could also be positive or detected in concurrent lymphocytic or histiocytic neoplasm.

[f]NGS sequencing studies are performed if clinically indicated, which may reveal BRAF-RAS-RAF-MEK-ERK pathway mutations in the MAPK pathway (eg, *KRAS, MAP2K1*) with or without additional somatic mutations also seen in myeloid neoplasia.

[g]If a familial RDD is suspected, germline mutations in *SLC29A3* should be considered. A germline gene mutation involving Fas gene *TNFRSF6*- found in 40% of RDD patients who had an ALPs type Ia.

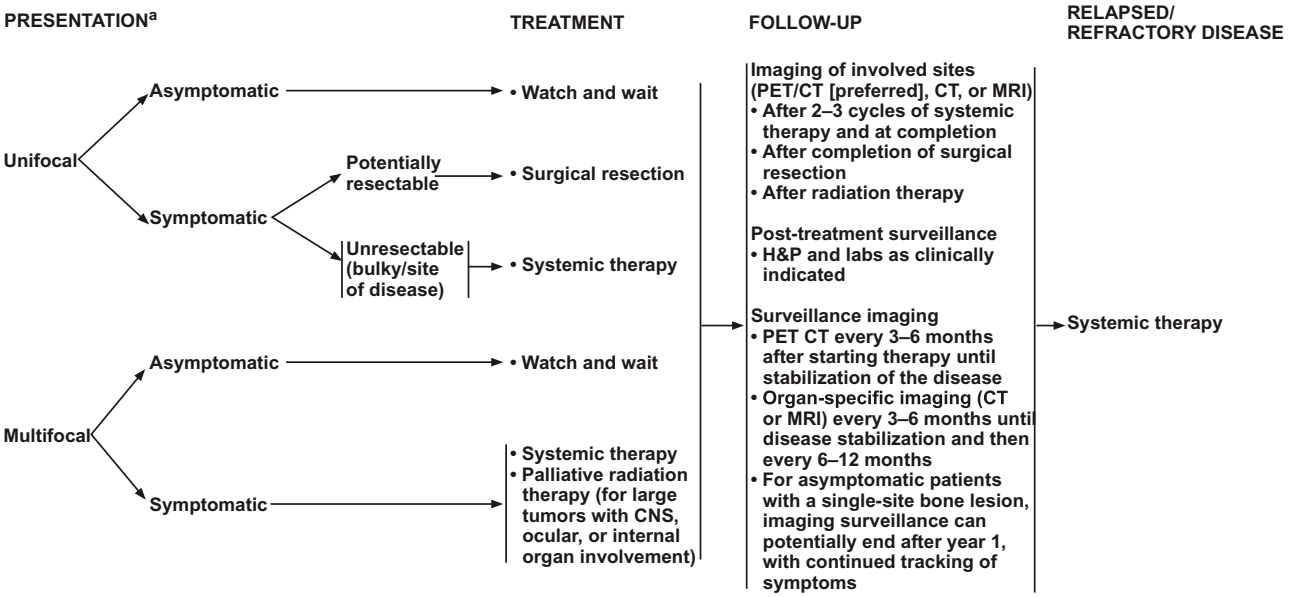
also support use of specific chemotherapy options for multifocal skin-involved LCH. A single-center retrospective study evaluated hydroxyurea monotherapy and in combination with oral methotrexate in 15 patients with relapsed/refractory LCH (mostly skin-involved) with a median age of 41.2 years (range, 2–73 years).[71] An ORR of 80.0% was observed, and symptom progression or relapse after initial response was observed in 40%, with median time to progression of 5.7 months. Grade 3 to 4 adverse events were reported in only 2 patients. Retrospective data also support use of oral methotrexate combined with prednisone in children with low-risk LCH (ie, no bone marrow involvement or organ dysfunction) that was mostly bone- and/or skin-involved.[72]

Immunomodulating agents may also be used to treat multifocal skin disease. Thalidomide was evaluated in a phase II study including 12 children and 4 adults with LCH.[73] Among 10 patients with low-risk disease (involvement of skin, lungs, and lymph nodes), an ORR of 70% was observed (4 CRs, 3 PRs). All of the patients but one who had low-risk disease had skin involvement. Administration of this drug was associated with significant toxicity and should be avoided in patients with critical organ involvement, for whom this drug was not effective. A case report also describes a CR from lenalidomide in an adult with relapsed/refractory multisystem LCH (involvement of skin, lungs, and lymph nodes).[74]

Targeted Therapies

Before 2012, there were relatively few effective treatment options for histiocytic neoplasms. The discovery of *BRAF* V600E and other gene mutations resulting in overactive MAPK pathway in histiocytic neoplasms led to a promising avenue of targeted therapies for patients with these rare cancers. The phase II VE-BASKET study evaluated the efficacy of BRAF inhibitor vemurafenib.[75] The final efficacy and safety analysis included 26 adults with *BRAF* V600E-mutated LCH or ECD (85% ECD) and showed an ORR of 61.5% (95% CI, 40.6%–79.8%).[76] Two-year PFS and OS rates were 86% (95% CI, 72%–100%) and 96% (95% CI, 87%–100%), respectively. Median PFS and OS were not reached. A metabolic response as measured with FDG-PET/CT was achieved in all of the patients who were evaluated (n=15; 80% CR, 20% PR). The most

Rosai-Dorfman Disease



[a]Adapted with permission from: Abla O, et al. Blood 2018;131:2877-2890.

common grade 3 to 4 adverse events were hypertension (27%), maculopapular rash (23%), increased lipase (15%), arthralgia (12%), hyperkeratosis (8%), and actinic keratosis (8%). All patients required dose reduction due to toxicities. Encouraging results from a case series also support the use of dabrafenib, a second-generation BRAF inhibitor, in adults with LCH. Dabrafenib may be better tolerated than vemurafenib based on this case series, although there was no prospective head-to-head comparison.[77] Use of dabrafenib in patients with ND-LCH led to rapid symptomatic and radiographic improvement.

There is also evidence supporting the use of MEK inhibitors for treatment of histiocytic neoplasms. The MEK inhibitor cobimetinib was evaluated in a phase II trial including 18 adult patients diagnosed with a histiocytic neoplasm (67% ECD, 11% LCH, 11% RDD, and 11% mixed histiocytosis).[31] The ORR was 89% (one-sided 90% CI, 73%–100%), with a CR having been observed in 72% of patients. Median DOR and PFS were not reached after a median follow-up of 11.9 months. The most common adverse events that led to a dose reduction were ejection fraction decrease (27.8%), rash (11.1%), and diarrhea (11.1%). Though a mutation in the MAPK pathway was detected in 83% of patients, the efficacy of cobimetinib was not limited to these patients, indicating that cobimetinib can be used in any patient with a histiocytic disorder for whom systemic therapy is indicated.

Use of the MEK inhibitor trametinib for treatment of LCH is supported by case series and case reports.[78–80] In one case report, a combination of dabrafenib and trametinib demonstrated a sustained response in an adult woman with *BRAF* V600E-mutated LCH.[81]

Adverse events in patients with histiocytic disorders treated with BRAF and MEK inhibitors are consistent with those observed in previously published studies (eg, rash, pyrexia),[24] but the VE-BASKET trial showed that rates of hypertension and skin-related adverse events were higher in histiocytic neoplasms than previously observed in patients with metastatic melanoma.[76]

Activating mutations in *CSF-1R* and rearrangements involving *RET* and *ALK* in rare cases of LCH highlight the potential clinical benefit of other kinase inhibitors and should be considered in select cases with such alterations.[46] Since *NTRK* fusions can occur in histiocytic

PRINCIPLES OF PATHOLOGY

General Principles

- **Langerhans cell histiocytosis (LCH), Erdheim-Chester disease (ECD), and Rosai-Dorfman disease (RDD) pose a diagnostic challenge given their rarity, their overlap with each other, reactive processes, and co-occurrence with other hematologic or non-hematologic neoplasms.**
- **Numerous site-specific mimics of histiocytoses exist due to relatively nonspecific appearance and immunophenotype, such as granular cell tumor, giant cell tumors of the bone and soft tissue, xanthogranulomas, and multicentric reticulohistiocytosis. Manifestations may also vary by site.[1,2]**
- **Comprehensive immunophenotyping should be performed including S100, CD1a, Langerin (CD207), CD68 and/or CD163, cyclin D1, *BRAF* V600E (VE1), factor XIIIa, and, if indicated, *ALK* and fascin. Discriminatory markers for carcinoma, melanoma, lymphoma, sarcoma, and other suspected disorders are useful for differential diagnoses. Cyclin D1 immunohistochemistry can be helpful to distinguish LCH from reactive Langerhans cell collections and has also been reported to be positive in RDD.[3-5]**
- **ALK immunohistochemistry may be considered, as *ALK*+ histiocytosis may carry a targetable *ALK* rearrangement.[6,7]**
- **It is recommended to perform molecular mutation profiling to aid in confirming a clonal Langerhans or histiocytic process and to identify potential prognostically relevant mutations or therapeutic targets. Correlation with clinical presentation and imaging findings is crucial for accurate diagnosis. Tissue diagnosis should be confirmed by pathologists with expertise in site-specific histiocytic lesions (eg, hematopathology, dermatopathology, pulmonary pathology, neuropathology).[8]**
- **In patients with unexplained cytopenias, bone marrow biopsy should be considered due to possible concomitant bone marrow processes, such as hemophagocytic lymphohistiocytosis or myeloid neoplasia. [9-14]**
- **For LCH and ECD, molecular testing for somatic mutations and fusions can be performed in a stepwise manner or in parallel, depending on clinical need and institutional protocols. The frequency of suspected molecular lesions should drive the order of testing if a stepwise algorithm is chosen. Allele-specific polymerase chain reaction (PCR) for *BRAF* V600E (VE1) mutations can be the first step if *BRAF* V600E (VE1) immunohistochemistry is not available or is equivocal. Somatic mutation NGS panel testing should cover the common MAPK pathway mutations. RNA-based molecular panel fusion testing should cover *BRAF*, *ALK*, and *NTRK1* rearrangements. If there is clinical concern for *ALK* rearrangement, or if fusion panel testing is not available, ALK immunohistochemistry and fluorescence in situ hybridization (FISH) studies may be performed.**

Langerhans Cell Histiocytosis

- **LCH is an abnormal proliferation of Langerhans-type cells with frequent driver mutations involving the MAPK pathway (RAS-RAF-MEK-ERK).**
- **Histopathologic features include cells with oval or twisted, grooved, or lobulated nuclei, finely granular chromatin, inconspicuous nucleoli, and abundant cytoplasm; these cells frequently have admixed eosinophils and histiocytes, including multinucleated forms, but not usually plasma cell rich. Ki-67 is variable.**
- **Langerhans cells show immunoreactivity for S100, CD1a, and Langerin (CD207).**
- **Reactive Langerhans cell infiltrates may mimic LCH; by immunohistochemistry, expression of cyclin D1 (Bcl1) and *BRAF* V600E (VE1 clone) support LCH.[6] VE1 staining is not 100% sensitive or specific, and concurrent molecular testing is recommended.**
- **Activating signaling pathway mutations found in LCH include *BRAF* V600E, *BRAF* indels, *MAP2K1*, *N/KRAS*, and *ARAF*. Kinase fusions (*BRAF, ALK, NTRK1*) and mutations in the PI3K-AKT-mTOR pathway have been reported in LCH as well.[15-17] Concomitant panel testing for *BRAF* V600E (VE1) and other MAPK pathway mutations is recommended.[18,19]**

Continued

References available at NCCN.org

disorders,[82] the TRK inhibitors larotrectinib[83] and entrectinib[84] may also be used as indicated. Sirolimus and everolimus can be effective for *PIK3CA*-mutated LCH, based on extrapolation of data from ECD patients (see "Treatment of ECD," page 1293).[7,85]

Follow-up

Imaging (PET/CT [preferred], CT, or MRI) of involved sites to evaluate treatment response should be done after 2 to 3 cycles of systemic therapy and after completion of treatment. LCH may relapse or reactivate after systemic therapy, which most commonly occurs in the first 2 years following treatment.[50] Development of diabetes insipidus after treatment may be a sign of disease reactivation.[50] Follow-up assessment depends on extent of disease and organ involvement, and a complete list of recommendations for surveillance following treatment of LCH can be found in the algorithm (see "Langerhans Cell Histiocytosis: Follow-up" in the algorithm [LCH-5, page 1283]).

Relapsed/Refractory Disease

In relapsed and refractory LCH, an alternate systemic therapy regimen other than the one used in the first line may be considered. However, if DOR to the first-line regimen was greater than 1 year, repeating the same treatment may also be considered.[14]

Erdheim-Chester Disease

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.[12,45,86] ECD predominantly affects adults, with a median age of approximately 45 years in the United States, and is more common in men than women.[12,45,86] ECD is rarely observed in children. Mixed ECD/LCH is fairly common, with LCH lesions reported in 20% of patients with ECD.[43]

Similar to LCH, ECD presentation can range from single system and asymptomatic disease to severe multisystem and life-threatening disease. Prognosis is predominantly influenced by specific organ involvement.[86] Bone involvement affects almost all patients with ECD, with lower extremity bone pain being an especially common initial presenting symptom. Cardiovascular involvement, including pericardial disease, is reported to occur

PRINCIPLES OF PATHOLOGY

Erdheim-Chester Disease

- Histopathologic features include foamy (xanthomatous) histiocytes, including Touton cells in a background of spindled cells and fibrosis. Reactive lymphocytes, plasma cells, and neutrophils are also often present. Typical histologic findings vary by site.[8] For example, bone lesions may be masked by significant fibrosis, including, in some cases, storiform fibrosis. In CNS and lung, the lesional histiocytes are non-lipidized, with eosinophilic cytoplasm, and lack the typical inflammatory infiltrate. In skin, the typical xanthomatous histiocytes are common but can be diffuse or interstitial and relatively subtle. In the retroperitoneum, findings are usually xanthomatous but sometimes extensively fibrotic, and can be associated with increased IgG4+ plasma cells meeting criteria for IgG4-related disease. Finally, in cardiac tissues, diffuse infiltrates of xanthomatous histiocytes may be observed.
- The neoplastic cells show immunoreactivities for some histiocytic markers (eg, CD68, CD163, fascin, and factor XIIIa). They are negative for CD1a and Langerin (CD207) and can be dim S100+.
- Activating signaling pathway mutations found in ECD are similar to those found in LCH, though *PIK3CA* activating mutation is more common in ECD. *BRAF* V600E mutation has been detected in about 50% of patients with ECD. Kinase fusions (*BRAF*, *ALK*, *NTRK1*) and *CSF1R* mutations have been reported rarely as well.[15,17,20] The revised histiocytic classification recommends classification of all "JXG" with activating MAPK pathway mutations (*BRAF, NRAS, KRAS, MAP2K1*) as ECD.[21,22]

Rosai-Dorfman Disease

- RDD comprises a heterogeneous group of clinical presentations that can be associated with familial, automimmune, or malignant process. Classical sporadic RDD shows bilateral painless massive cervical lymphadenopathy associated with B symptoms. It is often also found in mediastinal, inguinal, and retroperitoneal lymph nodes. Extranodal RDD presentation is not uncommon.
- Hallmark histopathologic features of nodal RDD include dilated sinusoidal spaces filled with large histiocytes with a round to oval hypochromatic nucleus, an inconspicuous to distinct nucleolus, and abundant foamy to clear cytoplasm engulfing a variable number of intact inflammatory cells—namely emperipolesis, a phenomenon recognized in either physiologic or pathologic process. Large histiocytes are positive for monocyte-macrophage markers (S100, CD68, CD163) and negative for LCH markers (CD1a, Langerin [CD207]). Cyclin D1/Bcl1 immunohistochemistry can be helpful to confirm the diagnosis. There are often increased polyclonal plasma cells, and further study is needed for confirmation of IgG4 disorder.[23] Extranodal RDD shows more fibrosis and less frequent emperipolesis.[24]
- A subset of patients with RDD harbor gene mutations involving *NRAS, KRAS, MAP2K1*, and rarely *BRAF*.[20,25,26]
- Inherited conditions predisposing to RDD are typically seen in pediatric cases but could be considered in adolescents and young adults:
  - Heterozygous germline gene mutation involving Fas gene *TNFRSF6*, which is found in 40% of RDD patients who had an ALPS type Ia.
  - *SLC29A3* germline gene mutation leading to familial or Faisalabad histiocytosis and H syndrome (histiocytosis-lymphadenopathy plus syndrome)
- Although RDD is not currently recognized by the WHO as a malignancy, some cases may truly be neoplastic with MAPK pathway driver mutations necessitating systemic therapies similar to other histiocytic neoplasms.

Continued

in about half of all patients[87–89] and is associated with poor prognosis.[90] Other affected organs/systems include the lungs, endocrine system, skin, and kidneys.[12,91] Periarterial fibrosis of the thoracic and/or abdominal aorta, referred to as "coated aorta," is also commonly obseved.[86,88,90,92–95] Retroperitoneal involvement tends to be asymptomatic, but extension to the renal sinus or middle to distal ureters may result in hydronephrosis.[96–98] CNS involvement occurs in 15% to 55% of cases[12,86,99] and is associated with worse prognosis.[100] Some ECD-related CNS lesions cause intracranial vascular infiltration, putting these patients at risk for ischemic stroke. Diabetes insipidus is the most common endocrine disorder in ECD, affecting about 25% to 50% of patients.[3,86,101] Other commonly observed endocrine manifestations of ECD include hyperprolactinemia, hypogonadism, adrenal insufficiency, and hypothyroidism.[3,101] Exophthalmos is also fairly common in ECD, and xanthelasma of the eyelids and periorbital spaces is a common cutaneous manifestation of ECD.[1,86] Involvement of the facial bones and maxillary sinuses has also been observed.[92]

Two retrospective studies demonstrated that a concomitant myeloid neoplasm can occur in 3%–10% of ECD[102,103]; the higher rate (10%) in one study is likely due to inclusion of patients with mixed LCH/ECD.[102] In one case series, median age of patients with ECD and a concomitant myeloid neoplasm was 65.4 years and tended to affect more men than women (male:female ratio = 2:1).[104]

Diagnosis of ECD

The diagnosis of ECD is largely made based on characteristic clinical and radiographic abnormalities. Evaluation of tumor tissue for molecular alterations should be performed, where available, as this would aid both in the diagnosis of ECD and treatment decision-making.[45] Comprehensive physical examination of the skin; HEENT; and cardiovascular, pulmonary, musculoskeletal, lymphatic, gastrointestinal, endocrine, neurologic systems should be performed. Neurocognitive and psychological assessments are also recommended in select patients. FDG-PET scan or bone scan should be used to evaluate bone involvement. Full-body (vertex-to-toes) FDG-PET is preferred to bone scan, as it allows for evaluation of metadiaphyseal osteosclerosis of the knees as well as other organ involvement.[3,45] Bilateral, symmetric diaphyseal, and metaphyseal osteosclerosis of the long bones of lower extremities is a characteristic finding of ECD.[2,3,12,45] CNS involvement may be detected using brain MRI with

SUMMARY OF PATHOLOGIC AND MOLECULAR FEATURES OF HISTIOCYTIC NEOPLASMS[1]

Disease	LCH	ECD	RDD
Pathologic features			
• Xanthomatous histiocytes	No	Yes	No
• Touton giant cells	No	Yes, (mainly dermal sites)	No
• Emperipolesis	No	Rare	Abundant
Cytologic features			
• Nuclei	• Oval; retiform,irregular nuclear contours or grooves	• Bland; round-to-oval; small; no grooves	• Large round; hypochromatic
• Nucleoli	• Inconspicuous	• Inconspicuous	• Variable inconspicuous to distinct
• Cytoplasm	• Abundant; eosinophilic	• Classically abundant, amorphous lipid-laden or granular/xanthomatous but often overlap with JXG/AXG	• Abundant foamy, clear without xanthomatous features; frequent emperipolesis
Background cells	• Increased eosinophils, eosinophilic microabscesses	• Inflammatory cells including few small lymphocytes and plasma cells, rare eosinophils, and dense, fibrosis	• Increased mature plasma cells, polyclonal, IgG4; occasional neutrophiils

JXG: juvenile xanthogranuloma; AXG: adult xanthogranuloma.

[1]Adapted with permission from Goyal G, Heaney ML, Collin M, et al. Erdheim-Chester disease: consensus recommendations for evaluation, diagnosis, and treatment in the molecular era. Blood 2020;135:1929-1945.

Continued

gadolinium contrast, and common findings include cerebellar and brain stem hyperintensities, cerebral white matter enhancement, and thickening of the pituitary stalk.[3,12] "Coated aorta" may be detected with CT, and arterial lesions characterized by circumferential thickening may be observed.[3,12,86,97] "Hairy kidney" detected on abdominal CT is characteristic of ECD (rarely seen in RDD and not seen in LCH) due to diffuse bilateral infiltration leading to stellate pattern of perinephric soft tissue thickening.[3,97] Adrenal hypertrophy may be observed if the perirenal infiltration extends to the adrenal gland.[97] In ECD with pulmonary involvement, chest CT may demonstrate mediastinal infiltration, pleural thickening, pleural effusion, and other pulmonary parenchymal abnormalities.[3] Cardiac involvement should be evaluated with echocardiography and/or cardiac MRI. Findings and radiographic abnormalities include pericardial thickening, pericardial effusion, and myocardial infiltration, which, if present, most often involve the right atrioventricular groove and right atrial wall.[3]

Similar to LCH, laboratory evaluation for ECD should include CBC, blood chemistry, coagulation studies, thyroid-stimulating hormone, free T4, morning urine and serum osmolality, morning serum cortisol with adrenocorticotropic hormone, prolactin, insulin-like growth factor-1, follicle-stimulating hormone/luteinizing hormone with testosterone, and estradiol. C-reactive protein should be evaluated, as it is often elevated in patients with ECD.[12] *BRAF* V600E (VE1) IHC is recommended on the tissue biopsy, and NGS of tumor tissue for mutations in the MAPK pathway in cases that are *BRAF* V600E wild-type or equivocal, as well as gene fusion assay, is also recommended (see "Pathologic Analysis of Histiocytic Neoplasms," page 1279, and "Histopathologic Characterization of ECD," page 1283). A biopsy of tumor tissue is recommended, but analysis of the peripheral blood for NGS may be done if biopsy is not feasible, and bone marrow evaluation should be performed in patients with abnormal CBC. Differential diagnosis should include evaluation for IgG4-related disease, which has a clinical presentation similar to that for ECD.[12]

The complete recommendations for evaluation of ECD are provided in the algorithm and are adapted from recommendations from an expert consensus group[45] (see ECD-1 in the algorithm [page 1284]). Subspecialty

SUMMARY OF PATHOLOGIC AND MOLECULAR FEATURES OF HISTIOCYTIC NEOPLASMS[1]

Disease	LCH	ECD	RDD
Molecular Features			
• *BRAF* V600E (VE1)	55%	50%	3%
• *MAP2K1*	15%	18%	15%
• RAS isoforms (*KRAS*, *NRAS*)	2%	8%	30%
• *BRAF* deletions	6%	2%	None
• PI3K isoforms (*PIK3CA, PIK3CD*)	1%	3%	None
• *ARAF*	1%	4%	3%
• Other *BRAF* missense	3%	None	None
• *RAF1*	None	1%	None
• *MAP2K2*	None	1%	None
• *MAP3K1*	Reported	(1 case) (Amplification)	None
• *CSF1R*	1%	1%	1%
• *BRAF* fusions	3%	2%	None
• *ALK* fusions	None	3%	None
• *NTRK1* fusions	None	1%	None
Immunophenotype			
• CD68 (cytoplasmic)	+ (paranuclear cytoplasmic dot)	++	++
• CD163 (surface)	—	++	++
• CD14 (surface)	—	++	++
• CD1a (surface)	++	—	—
• Langerin (CD207) (cytoplasmic)	++	—	—
• Cyclin D1	+	+/—	+/—
• S100 (cytoplasmic/nuclear)	+	+/—	+
• Factor XIIIa (cytoplasmic)	—	+	+/—
• Fascin (cytoplasmic)	—	+	+
• BRAF V600E (VE1) (cytoplasmic)[a]	+/—*	+/—*	— (Rare case reports++)
• ALK (cytoplasmic)[b]	—	+/—*	—
• NTRK1 (cytoplasmic)	—	+/—	—

Immunophenotype key: ++, strongly positive; +, weakly positive; +/—, positive or negative; —, negative.
*Moderate to strong positivity should correlate with molecular alteration; BRAF VE1, ALK, and phosphorylated tyrosine receptor kinase (pTRK) are mutually exclusive.

Footnotes
[a]Negative or equivocal immunohistochemistry for BRAF V600E (VE1) does not exclude mutated BRAF V600E. Test with NGS panel to cover the common mutations, including *BRAF*, *MAP2K1*, *NRAS*, *KRAS*.
[b]Testing *BRAF, ALK, and NTRK1* fusions is recommended if clinically histiocytosis is suspected and NGS panel testing does not reveal *BRAF* or other MAPK pathway mutations. Testing for somatic mutations using NGS first or in parallel is recommended.

[1]Adapted with permission from Goyal G, Heaney ML, Collin M, et al. Erdheim-Chester disease: consensus recommendations for evaluation, diagnosis, and treatment in the molecular era. Blood 2020;135(22):1929-1945.

consultations (eg, neurology, endocrinology, nephrology, urology) should be carried out as clinically indicated. As with LCH, dermatology and ophthalmology evaluations may be considered for management of toxicities associated with BRAF and MEK inhibitors.[30–32]

Histopathologic Characterization of ECD

On H&E stain, ECD tumor tissue often demonstrates foamy mononucleated histiocytes with a small nucleus, surrounding fibrosis, xanthogranulomatosis, and Touton giant cells.[2,3,12] On IHC, neoplastic histiocytes are typically CD68-positive, CD163-positive, CD14-positive, factor XIIIa-positive, CD1a-negative, and CD207 (langerin)-negative.[2,12,86] Typical features of stroma and histiocytic and reactive infiltrate have been found to vary depending on disease location (ie, bone, CNS, lung, skin, orbit, retroperitoneum, cardiac tissue).[105] CD1a-positive, S100-positive, and langerin-positive findings can help distinguish LCH from ECD.[1,86] The possible presence of S100-positive cells with emperipolesis may lead to challenges in distinguishing ECD from RDD.[1]

Somatic mutations contributing to ECD partially overlap with that of LCH.[2] *BRAF V600E* activating mutations are present in 38% to 68% of ECD cases.[6,7,86,92,105,106] Other prevalent gene mutations in ECD include *MAP2K1, ARAF, NRAS, KRAS,* and *PIK3CA.*[7,8,105,106] *CSF1R* mutations and *BRAF, ALK,* and *NTRK1* fusions are found in a small number of ECD cases.[8,46,106] ECD co-occurring with RDD is most commonly driven by mutations in *MAP2K1*.[105,107] Extracutaneous or disseminated juvenile xanthogranuloma with mutations in the *MAPK* pathway has similar histopathology and phenotype to ECD and thus may be considered ECD.[1] *BRAF* V600E (VE1) should be evaluated using IHC, but allele-specific PCR for *BRAF* V600E may be considered (see "Histopathologic Characterization of LCH," page 1283). As with LCH, panel testing should include other mutations in the MAPK pathway.

For complete recommendations regarding pathologic analysis of ECD cases, see the "Principles of Pathology" in the algorithm (HIST-A, page 1290).

Treatment of ECD

Treatment of ECD mainly consists of systemic therapy, though watch and wait may be considered for patients with asymptomatic disease not involving critical organs such as the heart, brain, and CNS.

PRINCIPLES OF SYSTEMIC THERAPY

Langerhans Cell Histiocytosis
• Regimens may be used in the first- or subsequent-line setting

	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Multisystem or pulmonary LCH	***BRAF* V600E mutated disease** • Vemurafenib[a,1,2] **MAP kinase pathway mutation, or no detectable mutation, or testing not available** • Cobimetinib[a,3] **Irrespective of mutation** • Cytarabine[4,5] • Cladribine[6,7] • Methotrexate + cytarabine[8]	***BRAF* V600E mutated disease** • Dabrafenib[a,2,9] **MAP kinase pathway mutation, or no detectable mutation, or testing not available** • Trametinib[a,9-13] **Irrespective of mutation** • Methotrexate (oral)[14,15] • Hydroxyurea[16] • Clofarabine[17] • Vinblastine/prednisone[4]	**Targeted therapy** • Crizotinib for *ALK* fusion[18] • Pexidartinib for *CSF1R* mutation[18] • Larotrectinib for *NTRK* gene fusion[19,20] • Entrectinib for *NTRK* gene fusion[19,21] • Sirolimus or everolimus for *PIK3CA* mutation[22,23] • Selpercatinib for *RET* fusion[18]
Bone disease only	• Zoledronic acid[24] • Pamidronate[24]	• None	Multifocal single-system bone disease not responsive to bisphosphonate • See preferred, other recommended, and useful in certain circumstances options above for multisystem disease
• Single-system multifocal skin disease (including mucosa)	• Methotrexate (oral)[14,15] • Hydroxyurea[16]	• Lenalidomide[25] • Thalidomide[26]	• None

[a]See Management of Toxicities Associated with Targeted Therapy (ME-K) in the NCCN Guidelines for Melanoma: Cutaneous†.

†To view the most recent version of these guidelines, visit NCCN.org.

Continued

As discussed in the LCH section (see "Targeted Therapies," page 1288), the phase II VE-BASKET study showed that vemurafenib is highly effective in patients with *BRAF* V600E-mutated ECD that is associated with near universal responses.[76] Results from the VE-BASKET study led to the FDA approval of vemurafenib for treatment of ECD. However, the FDA-approved dose (960 mg twice daily) is associated with significant toxicity that very often results in discontinuation, dose interruption, or dose modification.[76] A retrospective study performed at an NCCN Member Institution including 23 patients with *BRAF* V600E-mutated ECD showed that progressive disease did not occur in patients (n=14) who received vemurafenib administered at half the FDA-approved dose (ie, 480 mg twice daily), though half of these patients still required further dose reduction, with 29% discontinuing vemurafenib treatment due to adverse events.[108]

The efficacy of dabrafenib for *BRAF* V600E-mutated ECD is supported by a retrospective single-center French study[109] and a multicenter case series.[110] As with LCH, dabrafenib appears to be less toxic than vemurafenib.[110] As described previously for LCH (see "Targeted Therapies," page 1288), in a phase II trial in which 67% of patients were diagnosed with ECD, a 72% CR rate was shown for cobimetinib.[31] These promising results were not limited to patients with a mutation in the MAPK pathway. A small study supports use of the MEK inhibitor trametinib for treatment of non-LCH histiocytic neoplasms, regardless of molecular profile.[111]

Before the availability of targeted therapy for ECD, the largest body of evidence supported the use of interferon alpha-2a and pegylated interferon alpha for the treatment of ECD.[86] In a multicenter, prospective, nonrandomized study conducted in Europe (n=53), interferon alpha or pegylated interferon alpha treatment was associated with improved survival (hazard ratio [HR], 0.32; 95% CI, 0.14–0.70; P=.006).[100] A single-center report from France (n=8) showed that interferon alpha was most effective for relieving exophthalmos, bilateral hydronephrosis, and xanthelasma related to ECD, and was associated with a decrease in C-reactive protein.[112] This report cautioned against the use of interferon alpha in patients with ECD involving the CNS and/or cardiovascular system. However, a more recent single-center study from France reported outcomes of a larger cohort (n=24) that high-dose

PRINCIPLES OF SYSTEMIC THERAPY

Langerhans Cell Histiocytosis
• Regimens may be used in the first- or subsequent-line setting

	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
CNS lesions	***BRAF* V600E mutated disease** • Vemurafenib[a,1,2] **MAP kinase pathway mutation, or no detectable mutation, or testing not available** • Cobimetinib[a,3] **Irrespective of mutation** • Methotrexate + cytarabine[8] • Cladribine[6,7]	***BRAF* V600E mutated disease** • Dabrafenib[a,2,9] **MAP kinase pathway mutation, or no detectable mutation, or testing not available** • Trametinib[a,9,11-13] **Irrespective of mutation** • Cytarabine[b,4] • High-dose methotrexate[27]	**Targeted therapy** • Crizotinib for *ALK* fusion[18] • Pexidartinib for *CSF1R* mutation[18] • Larotrectinib for *NTRK* gene fusion[19,20] • Entrectinib for *NTRK* gene fusion[19,21] • Sirolimus or everolimus for *PIK3CA* mutation[22,23] • Selpercatinib for *RET* fusion[18]

[a]See Management of Toxicities Associated with Targeted Therapy (ME-K) in the NCCN Guidelines for Melanoma: Cutaneous†.
[b]Higher dose (150 mg/m^2) is indicated for CNS lesions.
†To view the most recent version of these guidelines, visit NCCN.org.

Continued

interferon alpha was associated with a clinical and/or radiologic improvement in 46% of patients, including those with severe ECD with CNS or cardiovascular involvement.[113] Interferon alpha as a treatment option for ECD is also supported by several case reports.[114,115] Interferon alpha has been discontinued in the United States and is therefore not recommended in the NCCN Guidelines. Pegylated interferon alpha, which has a favorable toxicity profile compared with interferon alpha, is recommended as a substitute based on evidence discussed previously.

Evidence supporting other systemic therapy options for treatment of ECD is primarily based on retrospective single-center studies and case series. A retrospective study conducted at an NCCN Member Institution evaluated the efficacy of cladribine as first- or subsequent-line treatment of ECD (n=21).[116] The clinical ORR was 52%, with CR and PR seen in 4% and 46% of patients, respectively. Progressive disease was seen in 30% of patients. The response was durable, with the median DOR of 9 months in the patients with response. Toxicities associated with cladribine were relatively minimal. In a single-center study from Italy including 10 patients with ECD, sirolimus combined with prednisone was associated with an ORR of 60% (all PRs).[117] Oral methotrexate as first- or subsequent-line treatment of ECD was evaluated in a retrospective study conducted at an NCCN Member Institution (n=13).[118] Oral methotrexate was administered either alone or in combination with prednisone or infliximab and was associated with a clinical ORR of 23% (all PRs). Progressive disease occurred in 70%. Despite the low ORR, methotrexate-based treatment was well-tolerated, and response was durable in some of those who responded to the treatment, especially those with ocular ECD. Finally, 2 small single-center studies showed good efficacy with the IL-1 receptor antagonist anakinra as a treatment option for ECD.[119,120]

As with LCH, a targeted therapy can be selected based on the respective molecular alteration. Crizotinib and selpercatinib for ECD with rearrangements in *ALK* and *RET*, respectively, as well as pexidartinib for ECD with activating mutations in *CSF-1R*, and larotrectinib and entrectinib for ECD with *NTRK* fusions, are all reasonable systemic therapy options when clinically indicated.[46,82–84] Because mutations in *PIK3CA* are fairly common in ECD,[7] mTOR inhibitors such as sirolimus

PRINCIPLES OF SYSTEMATIC THERAPY

Erdheim-Chester Disease
• Regimens may be used in the first- or subsequent-line setting

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
***BRAF* V600E mutated disease** • Vemurafenib[a,1,28] **MAP kinase pathway mutation, or no detectable mutation, or testing not available** • Cobimetinib[a,29] **Irrespective of mutation** • Cladribine[30] • Pegylated interferon alpha-2a and alpha-2b[31]	***BRAF* V600E mutated disease** • Dabrafenib[a,29,32] **MAP kinase pathway mutation, or no detectable mutation, or testing not available** • Trametinib[a,11,33] **Irrespective of mutation** • Sirolimus + prednisone[34] • Methotrexate (oral)[35] • Anakinra[a,36,37]	**Targeted therapy** • Crizotinib for *ALK* fusion[18] • Pexidartinib for *CSF1R* mutation[18] • Larotrectinib for *NTRK* gene fusion[19,20] • Entrectinib for *NTRK* gene fusion[19,21] • Sirolimus or everolimus for *PIK3CA* mutation[22,23] • Selpercatinib for *RET* fusion[18]

[a]See Management of Toxicities Associated with Targeted Therapy (ME-K) in the NCCN Guidelines for Melanoma: Cutaneous[†].

[†]To view the most recent version of these guidelines, visit NCCN.org.

Continued

and everolimus should also be considered when clinically indicated.[85]

Follow-up

As with LCH, follow-up assessment for patients with ECD depends on extent of disease and organ involvement. FDG-PET/CT should be used to monitor disease response once treatment is initiated. Organ-specific cross-sectional imaging (CT or MRI) may also be used as needed. Regular skin examination and ECG is recommended for patients treated with *BRAF* inhibitors, as well as ongoing evaluation for pituitary hormone abnormalities.

Rosai-Dorfman Disease

RDD is another rare histiocytic disorder that mainly affects children but is also diagnosed in adults. In RDD, accumulation of abnormal histiocytes in lymph node sinuses, lymphatic vessels of internal organs, and other extranodal sites is observed. This disease is more common in men than in women and often affects individuals of African ancestry.[12,121] Cause is unknown but may be associated with familial, autoimmune, and/or malignant processes. It is a heterogeneous condition with a presentation that may be classified as single or regional lymph node-involved or localized to the skin and other organs. Prognosis is generally very good but becomes worse as the number of involved nodal groups increases.[121] Recurrent disease is reported to occur in about one in three patients with RDD.[122]

Extranodal involvement occurs often in RDD, with common sites of involvement including the skin, soft tissue, upper respiratory tract, multifocal bone (mostly osteolytic lesions), retroperitoneum, and eye/retro-orbital tissue with lymphadenopathy.[3,121,122] Bilateral massive cervical lymphadenopathy also commonly occurs and is often painless, though involvement of the mediastinal, inguinal, and axillary lymph nodes may also occur.[121] Skin involved-RDD often presents as subcutaneous masses and, less often, as cutaneous lesions.[122] Involvement of the nasal cavity, paranasal sinuses, and parotid gland have also been reported.[12,121,123] CNS involvement may also occur but is generally rare.[121,122,124,125] CNS-involved RDD may mimic meningioma.[121]

RDD may co-occur with Hodgkin and non-Hodgkin lymphoma, other histiocytic disorders, cutaneous clear-cell sarcoma, and following myelodysplastic syndrome

PRINCIPLES OF SYSTEMIC THERAPY

Rosai-Dorfman Disease
• Regimens may be used in the first- or subsequent-line setting

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
MAP kinase pathway mutation, or no detectable mutation, or testing not available • Cobimetinib[a,38,39] Irrespective of mutation • Cladribine[40] • Cytarabine[41] • Methotrexate (oral)[42,43] • Prednisone or other corticosteroid[40]	MAP kinase pathway mutation, or no detectable mutation, or testing not available • Trametinib[a,11] Irrespective of mutation • Vinblastine + prednisone[44] • Methotrexate (IV)[45]	Targeted therapy • Crizotinib for *ALK* fusion[18] • Pexidartinib for *CSF1R* mutation[18] • Larotrectinib for *NTRK* gene fusion[19,20] • Entrectinib for *NTRK* gene fusion[19,21] • Everolimus for *PIK3CA* mutation[22,23] • Selpercatinib for *RET* fusion[18] • Sirolimus (for those associated with autoimmune lymphoproliferative syndrome and/or *PIK3CA* mutation)[22,23,46] Irrespective of mutation • Rituximab[c,d] (for nodal and immune-cytopenia diseases)[47] • Thalidomide (for cutaneous skin disease only)[48]

[a]See Management of Toxicities Associated with Targeted Therapy (ME-K) in the NCCN Guidelines for Melanoma: Cutaneous†.
[c]May be used for IgG4 disease.
[d]An FDA-approved biosimilar is an appropriate substitute for rituximab.

†To view the most recent version of these guidelines, visit NCCN.org.

References available at NCCN.org

and allogeneic stem transplant for precursor B-cell acute lymphoblastic leukemia.[12,121,122] Germline mutations in *SLC29A3*, which is associated with Faisalabad histiocytosis, H syndrome, and pigmented hypertrichotic dermatosis with insulin-dependent diabetes, have been found in cases of familial RDD.[121] About 20% of patients with H syndrome also have RDD.[126] Germline mutation in the *FAS* gene *TNFRSF*, which is associated with autoimmune lymphoproliferative syndrome (ALPS) type I, has also been found in RDD cases.[121] Immunologic diseases associated with RDD include systemic lupus erythematous, idiopathic juvenile arthritis, and autoimmune hemolytic anemia.[121]

Diagnosis of RDD

Diagnosis of RDD should include a clinical and radiologic examination, as well as histopathologic analysis. Comprehensive physical examination should include evaluation of the HEENT, endocrine system, and intrathoracic/pulmonary, cardiovascular, gastrointestinal, musculoskeletal genital, renal, and cutaneous symptoms. Neurologic and psychological assessment are also recommended. History of inherited conditions predisposing to RDD (eg, ALPS), malignancies and other neoplasia associated with RDD (eg, Hodgkin and non-Hodgkin lymphoma, other histiocytic disorders), and other autoimmune disorders (eg, systemic lupus erythematous, idiopathic juvenile arthritis) should be evaluated based on clinical symptoms and family history.

Full-body FDG-PET/CT is recommended as part of the baseline evaluation of RDD. A single-center retrospective study including 109 FDG-PET/CT scans in 27 patients with RDD showed that PET/CT detected lesions not recognized by anatomic cross-sectional imaging in 30% of patients with available prior CT or MRI (n=20).[127] Results of PET/CT scans also led to changes in treatment in 41% of patients. Cross-sectional imaging can reveal dermatologic involvement in the form of lobular soft tissue lesions in the subcutaneous space.[3] Pulmonary involvement in RDD tends to manifest as mediastinal lymphadenopathy, airway disease, pleural effusion, and cystic and interstitial lung disease.[128] Extranodal retroperitoneal involvement, if present, would appear in radiologic findings as wispy infiltration and/or renal hilar masses.[3] MRI of the head tends to be superior for evaluation of the sinuses and orbits, compared with PET/CT.[3]

MRI of the brain and spine is useful for identification of asymptomatic neurologic involvement.[121]

Laboratory evaluation should include CBC, comprehensive metabolic panel, coagulation studies, and an evaluation of C-reactive protein, uric acid, LDH, and serum immunoglobulins.[121] If autoimmune disease is suspected based on clinical examination, then laboratory evaluation should include antinuclear antigen, anti-neutrophil cytoplasmic antibodies, rheumatoid factor, and HLA-B27. The ALPS panel is clinically indicated in patients with autoimmunity and lymphadenopathy. Laboratory evaluation in patients with anemia should include a Coombs test, haptoglobin, reticulocyte count, and blood smear. Lumbar puncture should be carried out if there are brain lesions that cannot be biopsied due to location. Bone marrow aspirate and biopsy are recommended for patients with unexplained cytopenias or abnormal CBC.[121] As with LCH and ECD, biopsy of tumor tissue is recommended for diagnosis and NGS testing. If biopsy is not feasible, then peripheral blood analysis is reasonable. NGS of tumor tissue should include mutations in the MAPK pathway, and gene fusion assay (see "Pathologic Analysis of Histiocytic Neoplasms," page 1279, and "Histopathologic Characterization of RDD," next section).

The complete recommendations for evaluation of RDD are provided in the algorithm and are adapted from recommendations from an expert consensus group[121] (see Rosai-Dorfman Disease: Workup/Evaluation in the algorithm [RDD-1, page 1287]). Like LCH and ECD, dermatology and ophthalmology evaluations may be considered due to toxicities associated with BRAF and MEK inhibitors.[30–32]

Histopathologic Characterization of RDD

Compared with LCH and ECD, histopathologic analysis of RDD can be challenging, because RDD tissue tends to contain relatively few lesional cells.[122] Large histiocytic cells with hypochromatic nuclei and an abundant amount of pale cytoplasm are required for diagnosis or RDD.[1] Emperipolesis, specifically intracytoplasmic leukocytes, is a frequently observed feature of RDD.[1–3,12,121,122] However, emperipolesis may be observed less often in extranodal lesion tissue.[121] Abundant plasma cells in the medullary cords and around the venules is a hallmark of nodal RDD.[121] Other pathologic hallmarks include the accumulation of CD68-positive, CD163-positive, CD14-positive, and S100-positive histiocytic cells.[1–3,121,122] RDD histiocytes tend to be CD1a- and CD207-negative, which helps to distinguish from LCH.[121] Cyclin D1 expression by the abnormal histiocytes, and increased IgG4-positive plasma cells in the background inflammatory infiltrate, may also be found.[129,130]

Unlike LCH and ECD, *BRAF V600E* activating mutations are not commonly seen in patients with RDD.[3,12,121] *KRAS*, *MAP21K*, *ARAF*, and *NRAS* mutations have been found in patients with RDD.[8,121,131] Though the WHO does not classify RDD as a neoplasm, the presence of mutations in the MAPK/ERK pathway in about 1 in 3 patients and supports the categorization of RDD as a neoplasm.[122,131] As with LCH and ECD, NGS panel testing should include mutations in the MAPK pathway. Even though some of these mutations (eg, *BRAF* V600E) are less common in RDD, a comprehensive panel test is helpful for distinguishing RDD from other histiocytic neoplasms. Germline testing for *SLC29A3*, if familial RDD is suspected, and *TNFRSF* may be considered if clinically indicated.

For complete recommendations regarding pathologic analysis of RDD cases, see "Principles of Pathology" in the algorithm (HIST-A, page 1290).

Treatment of RDD

Watch and wait is a reasonable treatment strategy for patients with asymptomatic and mild disease, as spontaneous remission has been reported to occur 40% of these patients.[121,122] Surgery is also a reasonable curative option for those with isolated disease or for debulking of symptomatic disease of the CNS, sinuses, or airways.[121,122] Patients with extranodal disease impacting critical organs and those with serious RDD-related complications require treatment. Radiation therapy (RT) should only be used for palliative purposes in patients with multifocal symptomatic disease.[121] Case reports have shown some efficacy for RT when used to treat refractory disease in the eyelid and soft tissue of the cheek,[132] as well as RDD lesions causing airway obstruction.[133] RT dosing for RDD is not well-established, but 30 to 50 Gy may be used.[121,133]

Systemic Therapy

Systemic therapy is recommended for first-line treatment of symptomatic unresectable or multifocal disease and for treatment of relapsed/refractory disease. There is a dearth of research in this area, and some systemic therapy options that may be used for treating RDD are extrapolated from ECD.[122] The strongest evidence supporting systemic therapy options for adults with RDD comes from two single-center retrospective studies, both conducted at NCCN Member Institutions. The first study, conducted at Mayo Clinic (n=57), showed that corticosteroid treatment (most often prednisone) was associated with a 56% ORR in the first-line setting, with relapse occurring in 53% of patients, and a 67% ORR in the subsequent-line setting.[122] This study also showed that cladribine was the most commonly used systemic therapy for treatment of recurrent disease and was associated with a 67% ORR.[122] In the second study, which was

conducted at the University of Pennsylvania and included patients with massive lymphadenopathy (n=15), rituximab treatment was associated with a 64% PFS at 24 months (n=7) and a 40% ORR (PRs only), with complete resolution of symptoms when administered in the first-line setting (n=5).[134] This drug was generally well-tolerated.

Case reports support use of cytarabine and oral methotrexate for treatment of RDD, as well as thalidomide for cutaneous RDD.[135–138] A case report describing treatment of a pediatric patient with RDD supports use of methotrexate delivered intravenously,[139] although oral administration is generally used. Use of sirolimus, which has demonstrated efficacy in patients with ALPS,[140] is supported for treatment of RDD by a case report describing treatment of a pediatric patient with RDD and severe autoimmunity.[141]

Steroids may be used to treat patients with symptomatic nodal or cutaneous disease, for unresectable or multifocal extranodal disease, and/or for relief of symptoms from CNS- or orbit-involved disease.[121,122] As described previously, the Mayo Clinic study supports use of prednisone for treatment of RDD, both in the first- and subsequent-line settings.[122] This study showed that prednisone combined with 6-mercaptopurine and either methotrexate or azathioprine was also associated with disease response in the subsequent-line setting in patients with subcutaneous and lymph node involvement, and a PR was achieved in one patient who was treated with cyclophosphamide, vincristine, and prednisone. Prednisone combined with vinblastine is also supported by a case report describing treatment of a pediatric patient with RDD,[142] but this regimen is associated with increased risk of neuropathy in adults.[62] Optimal duration of steroid treatment is unknown at this time; treating to optimal response, followed by a slow taper, is a reasonable strategy.[121] Adverse effects from steroids should be carefully monitored, though these are generally well-tolerated.[122]

Evidence supporting use of targeted agents for RDD is evolving, particularly for MEK inhibitors, and some options may be used based on extrapolation of evidence for use in ECD and LCH. In a retrospective multicenter French study of lung-involved RDD, cobimetinib was associated with decreased lung infiltration and SUV_{max} values.[143] Cobimetinib is also supported by a case report describing treatment of a patient with RDD and a *KRAS* activating mutation.[144] The MEK inhibitor trametinib is also an option, regardless of molecular profile.[111] Just as with LCH and ECD, targeted systemic therapy options (ie, crizotinib for *ALK* rearrangements, selpercatinib for *RET* rearrangements, pexidartinib for activating mutations in *CSF-1R*, larotrectinib and entrectinib for *NTRK* fusions) may be recommended as clinically indicated.[46,82–84]

Follow-up

As with LCH and ECD, follow-up assessment for patients with RDD depends on extent of disease and organ involvement. A complete list of recommendations for surveillance after treatment of RDD can be found in the algorithm (see "Rosai-Dorfman Disease: Follow-up" in the algorithm [RDD-3, page 1289]).

References

1. Emile JF, Abla O, Fraitag S, et al. Revised classification of histiocytoses and neoplasms of the macrophage-dendritic cell lineages. Blood 2016; 127:2672–2681.
2. Durham BH. Molecular characterization of the histiocytoses: neoplasia of dendritic cells and macrophages. Semin Cell Dev Biol 2019;86:62–76.
3. Goyal G, Young JR, Koster MJ, et al. The Mayo Clinic Histiocytosis Working Group consensus statement for the diagnosis and evaluation of adult patients with histiocytic neoplasms: Erdheim-Chester disease, Langerhans cell histiocytosis, and Rosai-Dorfman disease. Mayo Clin Proc 2019;94:2054–2071.
4. Writing Group of the Histiocyte Society. Histiocytosis syndromes in children. Lancet 1987;1:208–209.
5. Badalian-Very G, Vergilio JA, Degar BA, et al. Recurrent BRAF mutations in Langerhans cell histiocytosis. Blood 2010;116:1919–1923.
6. Haroche J, Charlotte F, Arnaud L, et al. High prevalence of BRAF V600E mutations in Erdheim-Chester disease but not in other non-Langerhans cell histiocytoses. Blood 2012;120:2700–2703.
7. Emile JF, Diamond EL, Hélias-Rodzewicz Z, et al. Recurrent RAS and PIK3CA mutations in Erdheim-Chester disease. Blood 2014;124:3016–3019.
8. Diamond EL, Durham BH, Haroche J, et al. Diverse and targetable kinase alterations drive histiocytic neoplasms. Cancer Discov 2016;6: 154–165.
9. Chang KTE, Tay AZE, Kuick CH, et al. ALK-positive histiocytosis: an expanded clinicopathologic spectrum and frequent presence of KIF5B-ALK fusion. Mod Pathol 2019;32:598–608.
10. Guyot-Goubin A, Donadieu J, Barkaoui M, et al. Descriptive epidemiology of childhood Langerhans cell histiocytosis in France, 2000-2004. Pediatr Blood Cancer 2008;51:71–75.
11. Stålemark H, Laurencikas E, Karis J, et al. Incidence of Langerhans cell histiocytosis in children: a population-based study. Pediatr Blood Cancer 2008;51:76–81.
12. Haroche J, Cohen-Aubart F, Rollins BJ, et al. Histiocytoses: emerging neoplasia behind inflammation. Lancet Oncol 2017;18:e113–e125.
13. Vassallo R, Ryu JH, Schroeder DR, et al. Clinical outcomes of pulmonary Langerhans'-cell histiocytosis in adults. N Engl J Med 2002;346:484–490.
14. Girschikofsky M, Arico M, Castillo D, et al. Management of adult patients with Langerhans cell histiocytosis: recommendations from an expert panel on behalf of Euro-Histio-Net. Orphanet J Rare Dis 2013;8:72.
15. Tazi A. Adult pulmonary Langerhans' cell histiocytosis. Eur Respir J 2006;27:1272–1285.
16. Makras P, Terpos E, Kanakis G, et al. Reduced bone mineral density in adult patients with Langerhans cell histiocytosis. Pediatr Blood Cancer 2012;58:819–822.
17. Rigaud C, Barkaoui MA, Thomas C, et al. Langerhans cell histiocytosis: therapeutic strategy and outcome in a 30-year nationwide cohort of 1478 patients under 18 years of age. Br J Haematol 2016;174:887–898.
18. Aricò M, Girschikofsky M, Généreau T, et al. Langerhans cell histiocytosis in adults. Report from the International Registry of the Histiocyte Society. Eur J Cancer 2003;39:2341–2348.

19. Ma J, Laird JH, Chau KW, et al. Langerhans cell histiocytosis in adults is associated with a high prevalence of hematologic and solid malignancies. Cancer Med 2019;8:58–66.
20. Goyal G, Shah MV, Hook CC, et al. Adult disseminated Langerhans cell histiocytosis: incidence, racial disparities and long-term outcomes. Br J Haematol 2018;182:579–581.
21. Grois N, Fahrner B, Arceci RJ, et al. Central nervous system disease in Langerhans cell histiocytosis. J Pediatr 2010;156:873–881.e1.
22. Héritier S, Barkaoui MA, Miron J, et al. Incidence and risk factors for clinical neurodegenerative Langerhans cell histiocytosis: a longitudinal cohort study. Br J Haematol 2018;183:608–617.
23. Willman CL, Busque L, Griffith BB, et al. Langerhans'-cell histiocytosis (histiocytosis X)–a clonal proliferative disease. N Engl J Med 1994;331:154–160.
24. Allen CE, Merad M, McClain KL. Langerhans-cell histiocytosis. N Engl J Med 2018;379:856–868.
25. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood 2016;127:2375–2390.
26. Phillips M, Allen C, Gerson P, et al. Comparison of FDG-PET scans to conventional radiography and bone scans in management of Langerhans cell histiocytosis. Pediatr Blood Cancer 2009;52:97–101.
27. Albano D, Bosio G, Giubbini R, et al. Role of ^{18}F-FDG PET/CT in patients affected by Langerhans cell histiocytosis. Jpn J Radiol 2017;35:574–583.
28. Obert J, Vercellino L, Van Der Gucht A, et al. ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography in the management of adult multisystem Langerhans cell histiocytosis. Eur J Nucl Med Mol Imaging 2017;44:598–610.
29. Thingujam B, Yu YT, Lee JY, et al. Tumour-stage mycosis fungoides initially misdiagnosed as Langerhans cell histiocytosis. Pathology 2020;52:593–596.
30. Lamiaux M, Scalbert C, Lepesant P, et al. Severe skin toxicity with organ damage under the combination of targeted therapy following immunotherapy in metastatic melanoma. Melanoma Res 2018;28:451–457.
31. Diamond EL, Durham BH, Ulaner GA, et al. Efficacy of MEK inhibition in patients with histiocytic neoplasms. Nature 2019;567:521–524.
32. Urner-Bloch U, Urner M, Jaberg-Bentele N, et al. MEK inhibitor-associated retinopathy (MEKAR) in metastatic melanoma: long-term ophthalmic effects. Eur J Cancer 2016;65:130–138.
33. Collin M, Bigley V, McClain KL, et al. Cell(s) of origin of Langerhans cell histiocytosis. Hematol Oncol Clin North Am 2015;29:825–838.
34. Grois N, Prayer D, Prosch H, et al. Neuropathology of CNS disease in Langerhans cell histiocytosis. Brain 2005;128:829–838.
35. Chatterjee D, Vishwajeet V, Saikia UN, et al. CyclinD1 is useful to differentiate Langerhans cell histiocytosis from reactive Langerhans cells. Am J Dermatopathol 2019;41:188–192.
36. Shanmugam V, Craig JW, Hornick JL, et al. Cyclin D1 is expressed in neoplastic cells of Langerhans cell histiocytosis but not reactive Langerhans cell proliferations. Am J Surg Pathol 2017;41:1390–1396.
37. Berres ML, Merad M, Allen CE. Progress in understanding the pathogenesis of Langerhans cell histiocytosis: back to Histiocytosis X? Br J Haematol 2015;169:3–13.
38. Rollins BJ. Genomic alterations in Langerhans cell histiocytosis. Hematol Oncol Clin North Am 2015;29:839–851.
39. Berres ML, Lim KP, Peters T, et al. BRAF-V600E expression in precursor versus differentiated dendritic cells defines clinically distinct LCH risk groups. J Exp Med 2014;211:669–683.
40. Héritier S, Emile JF, Barkaoui MA, et al. BRAF mutation correlates with high-risk Langerhans cell histiocytosis and increased resistance to first-line therapy. J Clin Oncol 2016;34:3023–3030.
41. Satoh T, Smith A, Sarde A, et al. B-RAF mutant alleles associated with Langerhans cell histiocytosis, a granulomatous pediatric disease. PLoS One 2012;7:e33891.
42. Brown NA, Furtado LV, Betz BL, et al. High prevalence of somatic MAP2K1 mutations in BRAF V600E-negative Langerhans cell histiocytosis. Blood 2014;124:1655–1658.
43. Hervier B, Haroche J, Arnaud L, et al. Association of both Langerhans cell histiocytosis and Erdheim-Chester disease linked to the BRAFV600E mutation. Blood 2014;124:1119–1126.
44. Chakraborty R, Hampton OA, Shen X, et al. Mutually exclusive recurrent somatic mutations in MAP2K1 and BRAF support a central role for ERK activation in LCH pathogenesis. Blood 2014;124:3007–3015.
45. Goyal G, Heaney ML, Collin M, et al. Erdheim-Chester disease: consensus recommendations for evaluation, diagnosis, and treatment in the molecular era. Blood 2020;135:1929–1945.
46. Durham BH, Lopez Rodrigo E, Picarsic J, et al. Activating mutations in CSF1R and additional receptor tyrosine kinases in histiocytic neoplasms. Nat Med 2019;25:1839–1842.
47. Fisher KE, Cohen C, Siddiqui MT, et al. Accurate detection of BRAF p.V600E mutations in challenging melanoma specimens requires stringent immunohistochemistry scoring criteria or sensitive molecular assays. Hum Pathol 2014;45:2281–2293.
48. Phan DAT, Phung GB, Duong TT, et al. The value of BRAF VE1 immunoexpression in pediatric Langerhans cell histiocytosis [published online December 9, 2020]. Fetal Pediatr Pathol, doi: https://doi.org/10.1080/15513815.2020.1857483
49. Ballester LY, Cantu MD, Lim KPH, et al. The use of BRAF V600E mutation-specific immunohistochemistry in pediatric Langerhans cell histiocytosis. Hematol Oncol 2018;36:307–315.
50. Allen CE, Ladisch S, McClain KL. How I treat Langerhans cell histiocytosis. Blood 2015;126:26–35.
51. Laird J, Ma J, Chau K, et al. Outcome after radiation therapy for Langerhans cell histiocytosis is dependent on site of involvement. Int J Radiat Oncol Biol Phys 2018;100:670–678.
52. Heyd R, Strassmann G, Donnerstag F, et al. [Radiotherapy in Langerhans-cell histiocytosis. 2 case reports and review of the literature]. Rontgenpraxis 2000;53:51–61.
53. Sakai H, Ibe M, Takahashi H, et al. Satisfactory remission achieved by PUVA therapy in Langerhans cell histocytosis in an elderly patient. J Dermatol 1996;23:42–46.
54. Imafuku S, Shibata S, Tashiro A, et al. Cutaneous Langerhans cell histiocytosis in an elderly man successfully treated with narrowband ultraviolet B. Br J Dermatol 2007;157:1277–1279.
55. Hoeger PH, Nanduri VR, Harper JI, et al. Long term follow up of topical mustine treatment for cutaneous langerhans cell histiocytosis. Arch Dis Child 2000;82:483–487.
56. Kaneshima A, Yamaguchi S, Miyagi T, et al. Extracellular signal-regulated kinase activation of self-healing Langerhans cell histiocytosis: a case report. J Dermatol 2019;46:812–815.
57. Simko SJ, Garmezy B, Abhyankar H, et al. Differentiating skin-limited and multisystem Langerhans cell histiocytosis. J Pediatr 2014;165:990–996.
58. Schönfeld N, Frank W, Wenig S, et al. Clinical and radiologic features, lung function and therapeutic results in pulmonary histiocytosis X. Respiration 1993;60:38–44.
59. Chellapandian D, Makras P, Kaltsas G, et al. Bisphosphonates in Langerhans cell histiocytosis: an international retrospective case series. Mediterr J Hematol Infect Dis 2016;8:e2016033.
60. Montella L, Merola C, Merola G, et al. Zoledronic acid in treatment of bone lesions by Langerhans cell histiocytosis. J Bone Miner Metab 2009;27:110–113.
61. De Benedittis D, Mohamed S, Rizzo L, et al. Indomethacin is an effective treatment in adults and children with bone Langerhans cell histiocytosis (LCH). Br J Haematol 2020;191:e109–e113.
62. Cantu MA, Lupo PJ, Bilgi M, et al. Optimal therapy for adults with Langerhans cell histiocytosis bone lesions. PLoS One 2012;7:e43257.
63. Saven A, Burian C. Cladribine activity in adult Langerhans-cell histiocytosis. Blood 1999;93:4125–4130.
64. Goyal G, Abeykoon JP, Hu M, et al. Single-agent cladribine as an effective front-line therapy for adults with Langerhans cell histiocytosis. Am J Hematol 2021;96:E146–E150.
65. Simko SJ, Tran HD, Jones J, et al. Clofarabine salvage therapy in refractory multifocal histiocytic disorders, including Langerhans cell histiocytosis, juvenile xanthogranuloma and Rosai-Dorfman disease. Pediatr Blood Cancer 2014;61:479–487.
66. Cao XX, Li J, Zhao AL, et al. Methotrexate and cytarabine for adult patients with newly diagnosed Langerhans cell histiocytosis: a single arm, single center, prospective phase 2 study. Am J Hematol 2020;95:E235–E238.
67. Miao HL, Zhao AL, Duan MH, et al. Clinical presentation and prognostic analysis of adult patients with Langerhans cell histiocytosis with pulmonary involvement. BMC Cancer 2020;20:911.
68. Ho P, Smith C. High-dose methotrexate for the treatment of relapsed central nervous system Erdheim-Chester disease. Case Rep Hematol 2014;2014:269359.

69. Ehrhardt MJ, Karst J, Donohoue PA, et al. Recognition and treatment of concurrent active and neurodegenerative Langerhans cell histiocytosis: a case report. J Pediatr Hematol Oncol 2015;37:e37–e40.
70. Allen CE, Flores R, Rauch R, et al. Neurodegenerative central nervous system Langerhans cell histiocytosis and coincident hydrocephalus treated with vincristine/cytosine arabinoside. Pediatr Blood Cancer 2010;54:416–423.
71. Zinn DJ, Grimes AB, Lin H, et al. Hydroxyurea: a new old therapy for Langerhans cell histiocytosis. Blood 2016;128:2462–2465.
72. Womer RB, Anunciato KR, Chehrenama M. Oral methotrexate and alternate-day prednisone for low-risk Langerhans cell histiocytosis. Med Pediatr Oncol 1995;25:70–73.
73. McClain KL, Kozinetz CA. A phase II trial using thalidomide for Langerhans cell histiocytosis. Pediatr Blood Cancer 2007;48:44–49.
74. Szturz P, Adam Z, Rehák Z, et al. Lenalidomide proved effective in multisystem Langerhans cell histiocytosis. Acta Oncol 2012;51:412–415.
75. Hyman DM, Puzanov I, Subbiah V, et al. Vemurafenib in multiple nonmelanoma cancers with BRAF V600 mutations. N Engl J Med 2015;373:726–736.
76. Diamond EL, Subbiah V, Lockhart AC, et al. Vemurafenib for BRAF V600-mutant Erdheim-Chester disease and Langerhans cell histiocytosis: analysis of data from the histology-independent, phase 2, open-label VE-BASKET Study. JAMA Oncol 2018;4:384–388.
77. Hazim AZ, Ruan GJ, Ravindran A, et al. Efficacy of BRAF-inhibitor therapy in BRAF(V600E)-mutated adult Langerhans cell histiocytosis. Oncologist 2020;25:1001–1004.
78. Lorillon G, Jouenne F, Baroudjian B, et al. Response to trametinib of a pulmonary Langerhans cell histiocytosis harboring a MAP2K1 deletion. Am J Respir Crit Care Med 2018;198:675–678.
79. Messinger YH, Bostrom BC, Olson DR, et al. Langerhans cell histiocytosis with BRAF p.N486_P490del or MAP2K1 p.K57_G61del treated by the MEK inhibitor trametinib. Pediatr Blood Cancer 2020;67:e28712.
80. Papapanagiotou M, Griewank KG, Hillen U, et al. Trametinib-induced remission of an MEK1-mutated Langerhans cell histiocytosis [published online May 18, 2017]. JCO Precis Oncol, doi: https://doi.org/10.1200/PO.16.00070
81. Awada G, Seremet T, Fostier K, et al. Long-term disease control of Langerhans cell histiocytosis using combined BRAF and MEK inhibition. Blood Adv 2018;2:2156–2158.
82. Taylor J, Pavlick D, Yoshimi A, et al. Oncogenic TRK fusions are amenable to inhibition in hematologic malignancies. J Clin Invest 2018;128:3819–3825.
83. Drilon A, Laetsch TW, Kummar S, et al. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. N Engl J Med 2018;378:731–739.
84. Doebele RC, Drilon A, Paz-Ares L, et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. Lancet Oncol 2020;21:271–282.
85. van Bommel EFH, van der Zijden MA, Smak Gregoor PJH, et al. Sirolimus monotherapy for Erdheim-Chester disease. Acta Oncol 2019;58:901–905.
86. Diamond EL, Dagna L, Hyman DM, et al. Consensus guidelines for the diagnosis and clinical management of Erdheim-Chester disease. Blood 2014;124:483–492.
87. Haroche J, Cluzel P, Toledano D, et al. Images in cardiovascular medicine. Cardiac involvement in Erdheim-Chester disease: magnetic resonance and computed tomographic scan imaging in a monocentric series of 37 patients. Circulation 2009;119:e597–e598.
88. Brun AL, Touitou-Gottenberg D, Haroche J, et al. Erdheim-Chester disease: CT findings of thoracic involvement. Eur Radiol 2010;20:2579–2587.
89. Gianfreda D, Palumbo AA, Rossi E, et al. Cardiac involvement in Erdheim-Chester disease: an MRI study. Blood 2016;128:2468–2471.
90. Haroche J, Amoura Z, Dion E, et al. Cardiovascular involvement, an overlooked feature of Erdheim-Chester disease: report of 6 new cases and a literature review. Medicine (Baltimore) 2004;83:371–392.
91. Arnaud L, Pierre I, Beigelman-Aubry C, et al. Pulmonary involvement in Erdheim-Chester disease: a single-center study of thirty-four patients and a review of the literature. Arthritis Rheum 2010;62:3504–3512.
92. Estrada-Veras JI, O'Brien KJ, Boyd LC, et al. The clinical spectrum of Erdheim-Chester disease: an observational cohort study. Blood Adv 2017;1:357–366.
93. Serratrice J, Granel B, De Roux C, et al. "Coated aorta": a new sign of Erdheim-Chester disease. J Rheumatol 2000;27:1550–1553.
94. Cavalli G, Guglielmi B, Berti A, et al. The multifaceted clinical presentations and manifestations of Erdheim-Chester disease: comprehensive review of the literature and of 10 new cases. Ann Rheum Dis 2013;72:1691–1695.
95. Villatoro-Villar M, Bold MS, Warrington KJ, et al. Arterial involvement in Erdheim-Chester disease: A retrospective cohort study. Medicine (Baltimore) 2018;97:e13452.
96. Haroche J, Arnaud L, Amoura Z. Erdheim-Chester disease. Curr Opin Rheumatol 2012;24:53–59.
97. Dion E, Graef C, Haroche J, et al. Imaging of thoracoabdominal involvement in Erdheim-Chester disease. AJR Am J Roentgenol 2004;183:1253–1260.
98. Mazor RD, Manevich-Mazor M, Shoenfeld Y. Erdheim-Chester Disease: a comprehensive review of the literature. Orphanet J Rare Dis 2013;8:137.
99. Parks NE, Goyal G, Go RS, et al. Neuroradiologic manifestations of Erdheim-Chester disease. Neurol Clin Pract 2018;8:15–20.
100. Arnaud L, Hervier B, Néel A, et al. CNS involvement and treatment with interferon-α are independent prognostic factors in Erdheim-Chester disease: a multicenter survival analysis of 53 patients. Blood 2011;117:2778–2782.
101. Courtillot C, Laugier Robiolle S, Cohen Aubart F, et al. Endocrine manifestations in a monocentric cohort of 64 patients with Erdheim-Chester disease. J Clin Endocrinol Metab 2016;101:305–313.
102. Papo M, Diamond EL, Cohen-Aubart F, et al. High prevalence of myeloid neoplasms in adults with non-Langerhans cell histiocytosis. Blood 2017;130:1007–1013.
103. Goyal G, Ravindran A, Liu Y, et al. Bone marrow findings in Erdheim-Chester disease: increased prevalence of chronic myeloid neoplasms. Haematologica 2020;105:e84–e86.
104. Tzankov A, Kremer M, Leguit R, et al. Histiocytic cell neoplasms involving the bone marrow: summary of the workshop cases submitted to the 18th Meeting of the European Association for Haematopathology (EAHP) organized by the European Bone Marrow Working Group, Basel 2016. Ann Hematol 2018;97:2117–2128.
105. Ozkaya N, Rosenblum MK, Durham BH, et al. The histopathology of Erdheim-Chester disease: a comprehensive review of a molecularly characterized cohort. Mod Pathol 2018;31:581–597.
106. Janku F, Diamond EL, Goodman AM, et al. Molecular profiling of tumor tissue and plasma cell-free DNA from patients with non-Langerhans cell histiocytosis. Mol Cancer Ther 2019;18:1149–1157.
107. Razanamahery J, Diamond EL, Cohen-Aubart F, et al. Erdheim-Chester disease with concomitant Rosai-Dorfman like lesions: a distinct entity mainly driven by *MAP2K1*. Haematologica 2020;105:e5–e8.
108. Ruan GJ, Hazim A, Abeykoon JP, et al. Low-dose vemurafenib monotherapy in *BRAFV600E* -mutated Erdheim-Chester disease. Leuk Lymphoma 2020;61:2733–2737.
109. Cohen Aubart F, Emile JF, Carrat F, et al. Targeted therapies in 54 patients with Erdheim-Chester disease, including follow-up after interruption (the LOVE study). Blood 2017;130:1377–1380.
110. Bhatia A, Ulaner G, Rampal R, et al. Single-agent dabrafenib for $BRAF^{V600E}$-mutated histiocytosis. Haematologica 2018;103:e177–e180.
111. Janku F, Patel H, Raghavan VK, et al. MEK inhibition with trametinib in patients with non-Langerhans histiocytosis irrespective of BRAF mutation status. Blood 2019;134(Suppl_1):2319.
112. Haroche J, Amoura Z, Trad SG, et al. Variability in the efficacy of interferon-alpha in Erdheim-Chester disease by patient and site of involvement: results in eight patients. Arthritis Rheum 2006;54:3330–3336.
113. Hervier B, Arnaud L, Charlotte F, et al. Treatment of Erdheim-Chester disease with long-term high-dose interferon-α. Semin Arthritis Rheum 2012;41:907–913.
114. Esmaeli B, Ahmadi A, Tang R, et al. Interferon therapy for orbital infiltration secondary to Erdheim-Chester disease. Am J Ophthalmol 2001;132:945–947.
115. Suzuki HI, Hosoya N, Miyagawa K, et al. Erdheim-Chester disease: multisystem involvement and management with interferon-alpha. Leuk Res 2010;34:e21–e24.
116. Goyal G, Shah MV, Call TG, et al. Clinical and radiologic responses to cladribine for the treatment of Erdheim-Chester disease. JAMA Oncol 2017;3:1253–1256.
117. Gianfreda D, Nicastro M, Galetti M, et al. Sirolimus plus prednisone for Erdheim-Chester disease: an open-label trial. Blood 2015;126:1163–1171.
118. Goyal G, Shah MV, Call TG, et al. Clinical and radiological responses to oral methotrexate alone or in combination with other agents in Erdheim-Chester disease. Blood Cancer J 2017;7:647.

119. Cohen-Aubart F, Maksud P, Saadoun D, et al. Variability in the efficacy of the IL1 receptor antagonist anakinra for treating Erdheim-Chester disease. Blood 2016;127:1509–1512.
120. Goyal G, Shah MV, Call TG, et al. Efficacy of biological agents in the treatment of Erdheim-Chester disease. Br J Haematol 2018;183:520–524.
121. Abla O, Jacobsen E, Picarsic J, et al. Consensus recommendations for the diagnosis and clinical management of Rosai-Dorfman-Destombes disease. Blood 2018;131:2877–2890.
122. Goyal G, Ravindran A, Young JR, et al. Clinicopathological features, treatment approaches, and outcomes in Rosai-Dorfman disease. Haematologica 2020;105:348–357.
123. Juskevicius R, Finley JL. Rosai-Dorfman disease of the parotid gland: cytologic and histopathologic findings with immunohistochemical correlation. Arch Pathol Lab Med 2001;125:1348–1350.
124. Sandoval-Sus JD, Sandoval-Leon AC, Chapman JR, et al. Rosai-Dorfman disease of the central nervous system: report of 6 cases and review of the literature. Medicine (Baltimore) 2014;93:165–175.
125. Andriko JA, Morrison A, Colegial CH, et al. Rosai-Dorfman disease isolated to the central nervous system: a report of 11 cases. Mod Pathol 2001;14:172–178.
126. Molho-Pessach V, Ramot Y, Camille F, et al. H syndrome: the first 79 patients. J Am Acad Dermatol 2014;70:80–88.
127. Mahajan S, Nakajima R, Yabe M, et al. Rosai-Dorfman disease-utility of 18F-FDG PET/CT for initial evaluation and follow-up. Clin Nucl Med 2020;45:e260–e266.
128. Cartin-Ceba R, Golbin JM, Yi ES, et al. Intrathoracic manifestations of Rosai-Dorfman disease. Respir Med 2010;104:1344–1349.
129. Baraban E, Sadigh S, Rosenbaum J, et al. Cyclin D1 expression and novel mutational findings in Rosai-Dorfman disease. Br J Haematol 2019;186:837–844.
130. Deshpande V, Zen Y, Chan JK, et al. Consensus statement on the pathology of IgG4-related disease. Mod Pathol 2012;25:1181–1192.
131. Garces S, Medeiros LJ, Patel KP, et al. Mutually exclusive recurrent KRAS and MAP2K1 mutations in Rosai-Dorfman disease. Mod Pathol 2017;30:1367–1377.
132. Maklad AM, Bayoumi Y, Tunio M, et al. Steroid-resistant extranodal Rosai-Dorfman disease of cheek mass and ptosis treated with radiation therapy. Case Rep Hematol 2013;2013:428297.
133. Toguri D, Louie AV, Rizkalla K, et al. Radiotherapy for steroid-resistant laryngeal Rosai-Dorfman disease. Curr Oncol 2011;18:e158–e162.
134. Namoglu EC, Hughes ME, Plastaras JP, et al. Management and outcomes of sinus histiocytosis with massive lymphadenopathy (Rosai Dorfman Disease). Leuk Lymphoma 2020;61:905–911.
135. Nasseri E, Belisle A, Funaro D. Rosai-Dorfman disease treated with methotrexate and low-dose prednisone: case report and review of the literature. J Cutan Med Surg 2012;16:281–285.
136. Wang W, Sun J, Zhang W, et al. Successful treatment of intracranial Rosai-Dorfman disease with cytarabine and dexamethasone: case report and review of literature. Ann Hematol 2020;99:1157–1159.
137. Nadal M, Kervarrec T, Machet MC, et al. Cutaneous Rosai-Dorfman disease located on the breast: rapid effectiveness of methotrexate after failure of topical corticosteroids, acitretin and thalidomide. Acta Derm Venereol 2015;95:758–759.
138. Chen E, Pavlidakey P, Sami N. Rosai-Dorfman disease successfully treated with thalidomide. JAAD Case Rep 2016;2:369–372.
139. Inoue S, Onwuzurike N. Venorelbine and methotrexate for the treatment of Rosai-Dorfman disease. Pediatr Blood Cancer 2005;45:84–85., author reply 86.
140. Teachey DT, Greiner R, Seif A, et al. Treatment with sirolimus results in complete responses in patients with autoimmune lymphoproliferative syndrome. Br J Haematol 2009;145:101–106.
141. Cooper SL, Arceci RJ, Gamper CJ, et al. Successful treatment of recurrent autoimmune cytopenias in the context of sinus histiocytosis with massive lymphadenopathy using sirolimus. Pediatr Blood Cancer 2016;63:358–360.
142. Cohen-Barak E, Rozenman D, Schafer J, et al. An unusual co-occurrence of Langerhans cell histiocytosis and Rosai-Dorfman disease: report of a case and review of the literature. Int J Dermatol 2014;53:558–563.
143. Moyon Q, Boussouar S, Maksud P, et al. Lung involvement in Destombes-Rosai-Dorfman disease: clinical and radiological features and response to the MEK inhibitor cobimetinib. Chest 2020;157:323–333.
144. Jacobsen E, Shanmugam V, Jagannathan J. Rosai-Dorfman disease with activating KRAS mutation - response to cobimetinib. N Engl J Med 2017;377:2398–2399.

Individual Disclosures for the NCCN Histiocytic Neoplasms Panel

Panel Member	Clinical Research Support/ Data Safety Monitoring Board	Scientific Advisory Boards, Consultant, or Expert Witness	Promotional Advisory Boards, Consultant, or Speakers Bureau	Specialties
Robert Baiocchi, MD, PhD	Prelude Therapeutics, and Viracta Therapeutics, Inc.	Viracta Therapeutics, Inc.	SUNY Upstate Medical Center	Medical Oncology
Ilia Buhtoiarov, MD	None	None	None	Pediatric Oncology
Erin B. Butler, MD	None	None	None	Pediatric Oncology
Patrick K. Campbell, MD, PhD	None	None	None	Pediatric Oncology
Don W. Coulter, MD	None	None	None	Pediatric Oncology
Eli Diamond, MD	Third Rock Ventures	None	None	Neurology/Neuro-oncology
Aron Flagg, MD	None	None	None	Pediatric Oncology
Ronald S. Go, MD	None	None	None	Hematology/ Hematology Oncology
Aaron M. Goodman, MD	None	EUSA, and Seattle Genetics, Inc.	Curio Science	Hematology/ Hematology Oncology
Gaurav Goyal, MD	None	None	None	Hematology/ Hematology Oncology, and Medical Oncology
Dita Gratzinger, MD, PhD	None	None	None	Pathology
Paul C. Hendrie, MD, PhD	None	None	None	Hematology/ Hematology Oncology
Meghan Higman, MD, PhD	None	None	None	Hematology/ Hematology Oncology
Michael D. Hogarty, MD	None	None	None	Pediatric Oncology
Eric Jacobsen, MD	AbbVie, Inc.; Daiichi-Sankyo Co.; Merck & Co., Inc.; and Verastem Oncology	ADC Therapeutics; Bayer HealthCare; Janssen Pharmaceutica Products, LP; Novartis Pharmaceuticals Corporation; and Pharmacyclics	None	Medical Oncology
Filip Janku, MD, PhD	None	None	None	Medical Oncology
Reem Karmali, MD, MS	Bristol-Myers Squibb Company; Juno Therapeutics, Inc.; Kite Pharma; and Takeda Pharmaceuticals North America, Inc.	Janssen Pharmaceutica Products, LP	AstraZeneca Pharmaceuticals LP; BeiGene; Bristol-Myers Squibb Company; Juno Therapeutics, Inc.; Karyopharm Therapeutics, Inc.; Kite Pharma; and MorphoSys AG	Hematology/ Hematology Oncology
David Morgan, MD	None	None	None	Hematology/ Hematology Oncology
Ann C. Raldow, MD, MPH	Intelligent Automation, Inc., and ViewRay, Inc.	Institute for Clinical and Economic Review (ICER)	None	Radiotherapy/Radiation Oncology
Alexandra Stefanovic, MD	None	Kite Pharma	None	Hematology/ Hematology Oncology
Srinivas K. Tantravahi, MBBS, MRCP	Karyopharm Therapeutics, Inc.	Karyopharm Therapeutics, Inc.	None	Hematology/ Hematology Oncology
Kelly Walkovich, MD	None	None	None	Pediatric Oncology
Ling Zhang, MD	None	None	None	Pathology

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