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CONSENSUS RECOMMENDATIONS

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

Gaurav Goyal, MBBS; Jason R. Young, MD; Matthew J. Koster, MD; W. Oliver Tobin, MBBCh, PhD; Robert Vassallo, MD; Jay H. Ryu, MD; Caroline J. Davidge-Pitts, MBBCh; Maria D. Hurtado, MD; Aishwarya Ravindran, MBBS; Julio C. Sartori Valinotti, MD; N. Nora Bennani, MD; Mithun V. Shah, MD, PhD; Karen L. Rech, MD; and Ronald S. Go, MD; on behalf of the Mayo Clinic Histiocytosis Working Group

Abstract

Histiocytic neoplasms, a rare and heterogeneous group of disorders, primarily include Erdheim-Chester disease, Langerhans cell histiocytosis, and Rosai-Dorfman disease. Due to their diverse clinical manifestations, the greatest challenge posed by these neoplasms is the establishment of a diagnosis, which often leads to a delay in institution of appropriate therapy. Recent insights into their genomic architecture demonstrating mitogen-activated protein kinase/extracellular signal–regulated kinase pathway mutations have now enabled potential treatment with targeted therapies in most patients. This consensus statement represents a joint document from a multidisciplinary group of physicians at Mayo Clinic who specialize in the management of adult histiocytic neoplasms. It consists of evidence- and consensus-based recommendations on when to suspect these neoplasms and what tests to order for the diagnosis and initial evaluation. In addition, it also describes the histopathologic and individual organ manifestations of these neoplasms to help the clinicians in identifying their key features. With uniform guidelines that aid in identifying these neoplasms, we hope to improve the awareness that may lead to their timely and correct diagnosis.

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Histiocytic neoplasms are rare neoplasms (annual incidence of <5 cases per million population) originating from cells of the myeloid lineage and primarily include Erdheim-Chester disease (ECD), Langerhans cell histiocytosis (LCH), and Rosai-Dorfman disease (RDD), but also several other disorders.[1] Although ECD is mainly a disease of young adults (median age, 45 years), LCH and RDD may be seen in all age groups. These neoplasms may present clinically as focal or diffuse multiple organ disease. The disease spectrum varies from incidental lesions on imaging studies to critical illness arising from severe organ dysfunction.

Historically, ECD and LCH were considered predominantly inflammatory diseases. The demonstration of clonal Langerhans cells in nonpulmonary LCH led to its designation

From the Division of Hematology (G.G., N.N.B., M.V.S., R.S.G.), Department of Radiology (J.R.Y.), Division of Rheumatology (M.J.K.), Department of Neurology (W.O.T), Division of Pulmonary and Critical Care Medicine (R.V., J.H.R.), Division of Endocrinology, Diabetes,

Affiliations continued at the end of this article.

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as a neoplastic process.[2] This was subsequently supported by the discovery of *BRAF* V600E mutations in more than 50% of patients with LCH 2 decades later.[3] More robust evidence for the clonal origin of LCH, as well as ECD, was brought to light by the demonstration of recurrent activating mutations in the mitogen-activated protein kinase/extracellular signal–regulated kinase (MAPK/ERK) pathway in more than 90% of the patients.[4] This has led to their inclusion in the 2016 World Health Organization classification of hematopoietic and lymphoid tumors.[5] Recently, similar MAPK/ERK pathway mutations were reported in 33% of patients with RDD as well, suggesting a clonal origin in a subset of these patients.[6,7] Discovery of such alterations also has therapeutic implications and led to the first Food and Drug Administration approval of a drug (vemurafenib) for the treatment of *BRAF* V600–mutant ECD.[8]

Owing to their rarity and diverse clinical manifestations mimicking other conditions, histiocytic neoplasms pose a major diagnostic challenge for many clinicians. The diagnosis is frequently delayed, often after multiple attempts at tissue biopsies of critical anatomical areas. Due to the high symptom burden related to pain or organ dysfunction, patients with these neoplasms generally receive empiric treatments resulting in adverse effects, and sometimes serious complications. A lack of diagnosis or misdiagnosis is common, which can be both frustrating for the clinician and psychologically disabling for the patients and their families. Suspecting these diseases in the appropriate clinical context and establishing a diagnosis are usually the greatest challenges. Hence, there is a need for the development of evidence- and experience-based guidelines for the diagnosis and evaluation of these rare disorders. In this context, we recently established the multidisciplinary Histiocytosis Working Group within Mayo Clinic, which led to the formulation of the consensus guidelines presented herein. We focused specifically on ECD, LCH, and RDD because they are the most commonly seen histiocytic neoplasms in adults and share similar biological pathways.

METHODS

The multidisciplinary group meetings began in June 2017 and included experts in various subspecialties who were engaged in the evaluation and management of patients with histiocytic neoplasms for several years. Owing to the multifaceted presentation of these disorders, the group consisted of experts from dermatology, endocrinology, hematology, laboratory medicine, neurology, pathology, pulmonology, radiology, and rheumatology. A primary task undertaken by this multidisciplinary group was to develop a uniform and practical approach to assist clinicians with the diagnosis of these entities. Once a diagnosis is established, patients and clinicians can benefit from input provided by centers of excellence regarding further management.

Each member of the multidisciplinary group contributed to a section on the manifestations of ECD, LCH, and RDD pertinent to their subspecialty by review of existing literature as well as experience with our own patient cohort. The data from the Mayo cohort were provided in situations in which they addressed gaps in the existing knowledge or countered the prevailing notions. The proposed recommendations were discussed at monthly group meetings to establish a consensus. Owing to the relative paucity of prospective studies in adult histiocytic disorders, the recommendations were not graded similar to guidelines for other diseases. These recommendations are specifically focused on the evaluation of adult patients with suspected histiocytic neoplasms to aid in diagnosis and are not aimed at discussing therapeutic recommendations or baseline evaluation of a newly diagnosed patient. The latter require comprehensive evaluation, and such recommendations already exist.[9-11] The following sections provide an in-depth review of the common as well as uncommon organ system manifestations of each disorder, which may help in specific clinical scenarios to arrive at a diagnosis. The key features of individual neoplasms are listed in Table 1 and depicted in Figures 1 through 3.

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TABLE 1. Key Features of Histiocytic Neoplasms Based on the Literature and the Mayo Clinic Cohort

Feature	ECD	LCH	RDD
Organ involvement (frequency and characteristic features)			
Bones	95% (pathognomonic long-bone osteosclerosis at the metadiaphysis)	60% (osteolytic lesions including skull)	15% (cortex-based osteolytic lesions most common)
Nervous system	40% (brainstem/cerebellum masses; cerebral white matter enhancement; dural and pituitary stalk thickening)	5% (MRI with globus pallidus/dentate nucleus T1 hyperintensity; brainstem/cerebellum T2 hyperintensity; dural lesion from intracranial extension of skull lesion; pituitary stalk thickening)	10% (isolated dural or parenchymal lesion)
Endocrine	40%-70% DI 40% (may present years before diagnosis of ECD)	40%-70% DI 20%-30% (may present years before diagnosis of LCH)	Rarely reported DI never reported
Respiratory	50% (mediastinal infiltration; pleural, septal, and maxillary sinus thickening)	50%-60% (mostly seen in smokers; HRCT shows pulmonary nodules in the early stage, cysts in the later stage)	10%-20% (primarily involving large airways and sinuses; rarely interstitial pulmonary or sinus thickening; pleural or pulmonary nodule)
Dermatologic	25% (xanthelasma-like lesions around eyes, face, neck, inguinal folds)	15%-30% (papular rash; rarely subcutaneous nodules or xanthelasma-like lesions)	50% (more common subcutaneous nodules, may be seen as macular or papular rash)
Cardiac	40%-70% (right atrial and atrioventricular groove infiltration; pericardial and myocardial infiltration seen on cardiac MRI)	Rarely reported	<5% (infiltration of the right atrium, interatrial septum, and left ventricle)
Arterial	50%-80% (periaortic infiltration "coated aorta"; infiltration of the supra-aortic trunk branches, visceral arteries, renal artery stenosis, coronary arteries)	Rarely reported	<5% (infiltration of the periaortic and carotid sheath)
Retroperitoneum, including kidneys	40%-50% (perinephric infiltration "hairy kidneys" with extension to renal pelvis and ureters causing renal failure; adrenal infiltration)	Rarely reported	5%-10% (commonly hilar masses; subcapsular infiltration; rarely perinephric coating)
Lymph nodes	Never reported	5%-10% (rarely isolated)	30%-50% (may present as isolated or generalized lymphadenopathy)
Orbits	30% (orbital masses)	Never reported	5% (orbital masses, sometimes involving the optic nerve)
Histopathologic characteristics[a]			
CD68	+	+	−/+
CD163	+	−/+	+
S100	−/+	+/−	+
CD1a	−	+	−
Langerin	−	+	−
Factor XIIIa	+	−	−/+
BRAF V600E[b]	+/−	+/−	−

[a]When positive, the immunohistochemical markers generally highlight all the lesional histiocytes of ECD, RDD, and LCH while being negative in the background reactive infiltrate. Patients with overlap disease (ECD-LCH or ECD-RDD) may present with features of both disorders.

[b]*BRAF* V600E testing by immunohistochemical analysis may have insufficient sensitivity to detect the mutant protein in histiocytic neoplasms. Molecular testing methods are recommended to definitely exclude a mutation.

DI= diabetes insipidus; ECD = Erdheim-Chester disease; HRCT= high-resolution computed tomography; LCH = Langerhans cell histiocytosis; MRI= magnetic resonance imaging; RDD = Rosai-Dorfman disease.

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ORGAN INVOLVEMENT: CLINICAL AND RADIOGRAPHIC CHARACTERISTICS

Bones

In ECD, lower extremity bone pain is one of the most common presenting symptoms, occurring in approximately 50% of patients.[12] Ill-defined bilateral symmetrical osteosclerosis of the metadiaphyseal bones around the knees is very common (>95%) and pathognomonic of ECD.[13] However, involvement of the axial skeleton and even the small bones of the feet can be seen (47% and 9%, respectively).[14] Reports of complications from bone involvement are scant, with 3 cases of nontraumatic fracture in the literature, 2 of which might have been insufficiency fractures.[15-17] Although whole-body bone scintigraphy is a sensitive screening test for ECD bone involvement, 18F-fluorodeoxyglucose (FDG) positron emission tomography—computed tomography (PET-CT) can be even more sensitive, with the ability to detect subtle vertebral involvement and the added benefit of directing the biopsy site.[14,18-21]

Adult LCH commonly involves bones and may occur as a bone-limited disease (38%) or as a component of multisystem disease (66%).[22] The skull is most commonly involved, followed by the axial and proximal appendicular skeleton.[23,24] Bone involvement usually manifests as pain or as a mass/swelling of the involved site.[25] Aggressive radiographic patterns of bone involvement are more common, with "moth-eaten" permeative and cortically based lytic lesions that may progress with possible laminated periosteal reaction, prone to fracture. As with ECD, PET-CT has overall superior detection of LCH bone lesions compared with conventional imaging such as radiographs, computed tomography (CT), and magnetic resonance imaging (MRI).[26-28] However, MRI is superior in evaluating subtle vertebral lesions.[26] Bone scintigraphy has little role in imaging for LCH.[29]

In contrast, bone involvement in RDD is less common (10%-20%) and rarely occurs in isolation.[30,31] When present, RDD of the bone is usually evident clinically as pain, compressive neuropathy with spinal disease, or headache with skull involvement.[32] Skeletal RDD lesions are usually lytic, yet less aggressive and centered in the medullary space. A unique feature is the lack of periosteal reaction and large soft tissue components.[32] Our preferred imaging evaluation for RDD bone disease is similar to that for LCH with PET-CT owing to increasing evidence of its utility.[33-44]

Neurologic

The identification of central nervous system (CNS) involvement in histiocytic neoplasms is important because it may be associated with an increased risk of mortality, especially in ECD.[45] Note that in some patients, asymptomatic or paucisymptomatic central and peripheral nervous system involvement can be observed.

Erdheim-Chester disease has a predilection for the posterior fossa brain parenchyma and spinal cord; however, it can also be associated with pituitary, dural, facial sinus, and orbital involvement.[46] Involvement of the CNS occurs in approximately 40% of patients with ECD, with clinical and radiologic signs/symptoms occurring in as many as 90%.[13,46] Cognitive impairment, ataxia, and peripheral neuropathy occur in approximately 40% to 50% of patients. Headaches are present in 20% of patients.[13] White matter T2 hyperintensities, with and without postgadolinium enhancement, are common and likely result from direct tumor infiltration, small vessel disease, or a neurodegenerative process. Patients without evidence of intracranial ECD have a reduction in gray matter volumes on volumetric analysis independent of treatment and intracranial disease, raising the possibility of a secondary neurodegenerative process.[47]

Langerhans cell histiocytosis is associated with T2 hyperintense, gadolinium-enhancing lesions most commonly of the pituitary stalk, pineal gland, and other circumventricular regions (5%-10%).[48] Parenchymal involvement can occur but is rare. Symmetrical, T2 hyperintense signal changes and hypointense or hyperintense signals on T1 can also be seen in the cerebellar gray matter, pons, basal ganglia, and globus

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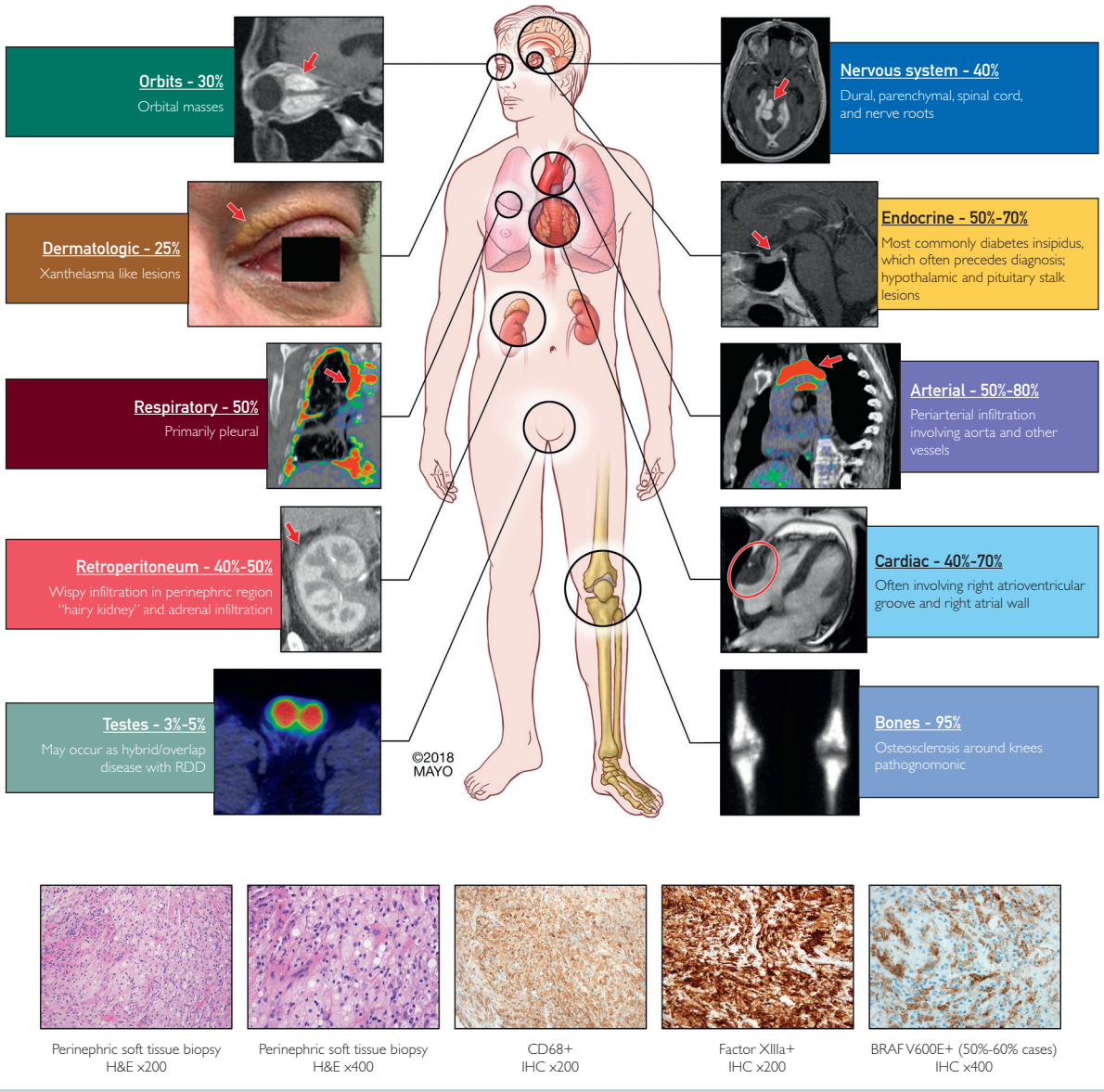


FIGURE 1. Key features of Erdheim-Chester disease. The illustration depicts clinical and radiographic features with frequencies and descriptions (top) and histopathologic features (bottom). H&E = hematoxylin and eosin; IHC = immunohistochemistry; RDD = Rosai-Dorfman disease.

pallidum.[49] These lesions show variable FDG uptake, in contrast to tumefactive lesions,[50,51] and can be asymptomatic or associated with progressive neurologic decline. The term *neurodegenerative histiocytosis* has been given to the MRI signal abnormalities and neurologic dysfunction associated primarily with LCH; some of these patients may have minimal or no clinical neurologic symptoms.[49]

Rosai-Dorfman disease involving the CNS is rare (10%) and involves the dura far more frequently than the brain parenchyma.[31,52] A potential clue to the diagnosis is emperipolesis (lymphocytes engulfed by histiocytes) in spinal fluid.[53]

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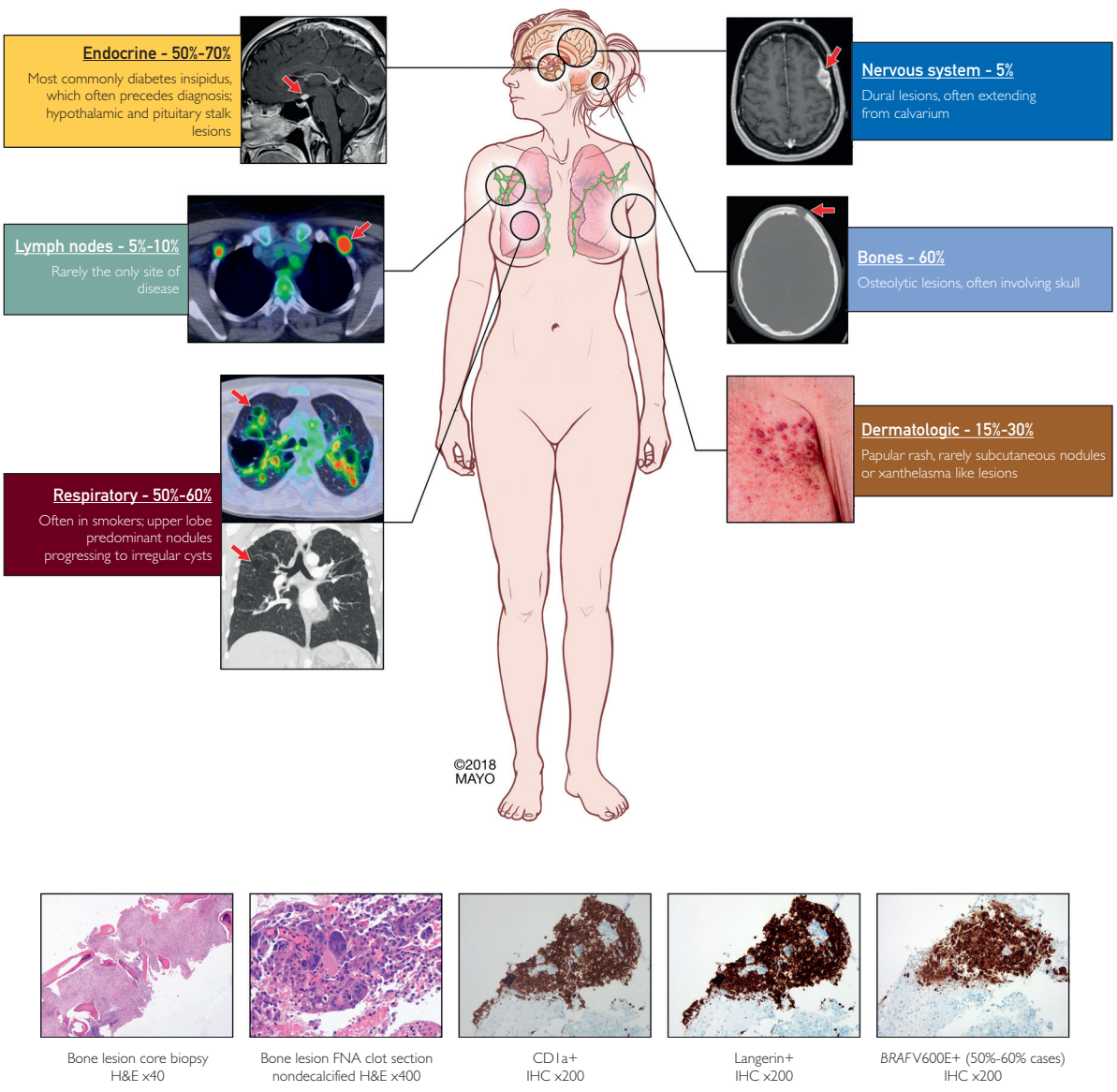


FIGURE 2. Key features of Langerhans cell histiocytosis. The illustration depicts clinical and radiographic features with frequencies and descriptions (top) and histopathologic features (bottom). FNA = fine-needle aspiration; H&E = hematoxylin and eosin; IHC = immunohistochemistry.

Endocrine

Endocrine manifestations are relatively common, particularly in ECD and LCH, and may commonly lead to permanent endocrinopathies in these patients.[54,55] Infiltration of the hypothalamus or pituitary may lead to impairment of both the anterior and posterior pituitary hormones in 40% to 70% of patients. Hence, all patients with ECD and LCH should undergo endocrine evaluation at baseline and during follow-up (Figure 4). Growth hormone and corticotropin deficiencies may require dynamic testing for definitive diagnosis. Histiocytic neoplasms may also increase the risk of bone and metabolic abnormalities, and patients may benefit from screening for these complications at the time of diagnosis.

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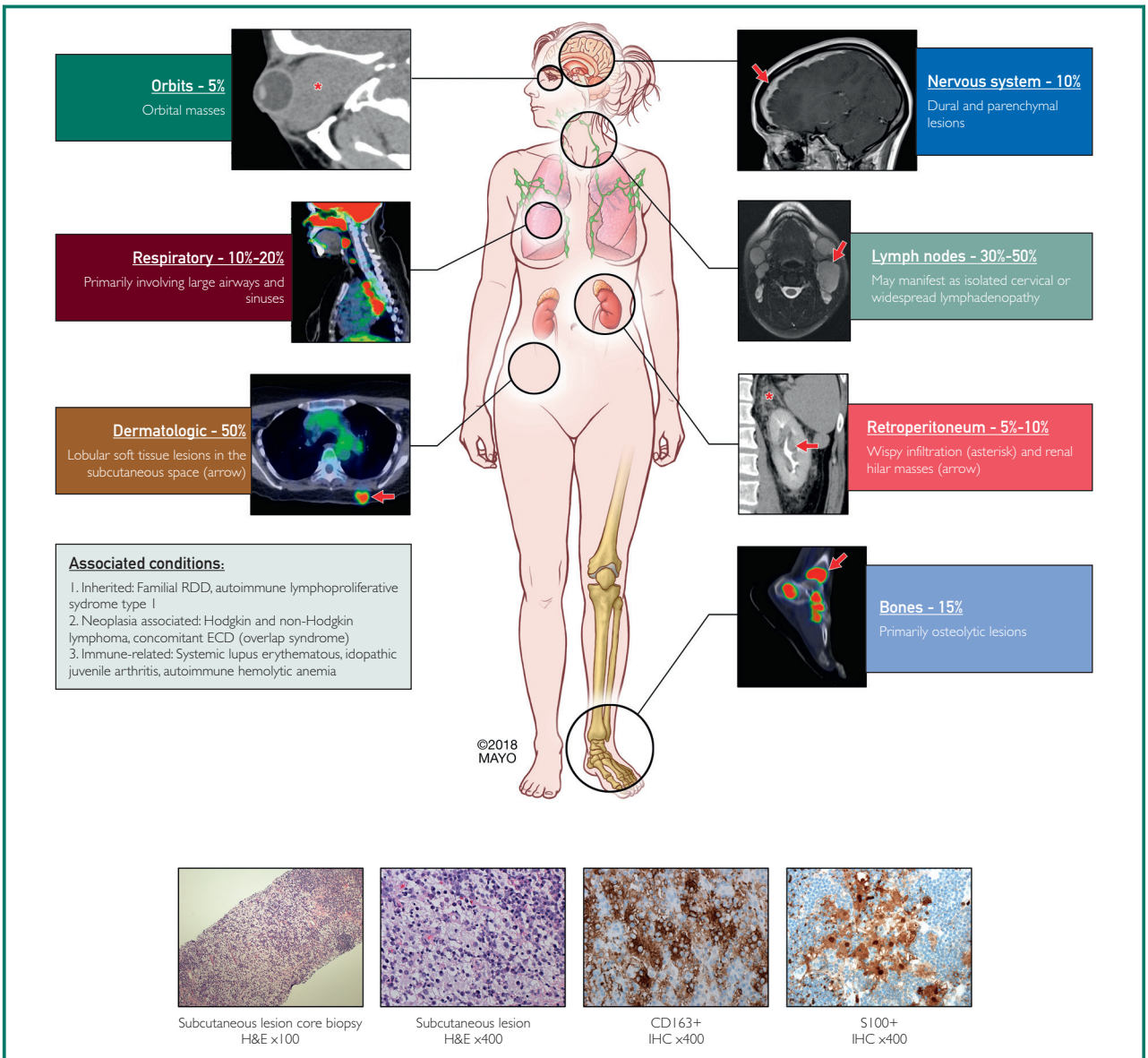


FIGURE 3. Key features of Rosai-Dorfman disease (RDD). The illustration depicts clinical and radiographic features with frequencies and descriptions (top) and histopathologic features (bottom). ECD = Erdheim-Chester disease; H&E = hematoxylin and eosin; IHC = immunohistochemistry.

The most common presenting endocrine disorder in ECD is diabetes insipidus (DI). The prevalence of DI in ECD ranges from 25% to 50% and may precede the diagnosis by many years.[55-57] It is associated with anterior pituitary hormonal deficiencies in more than 50% of patients,[58,59] and patients can have anterior hormone deficiencies without DI. In one study, the most common anterior pituitary deficit was growth hormone (79%), followed by gonadotropin (22%), thyrotropin (10%), and corticotropin (3%) deficiencies. Hyperprolactinemia is found in approximately 40% of patients.[55] Normal pituitary imaging does not necessarily exclude hormonal deficiency. However, most patients with abnormal pituitary stalk MRIs have hypopituitarism.

In addition to the hypothalamic/pituitary involvement, ECD can infiltrate peripheral

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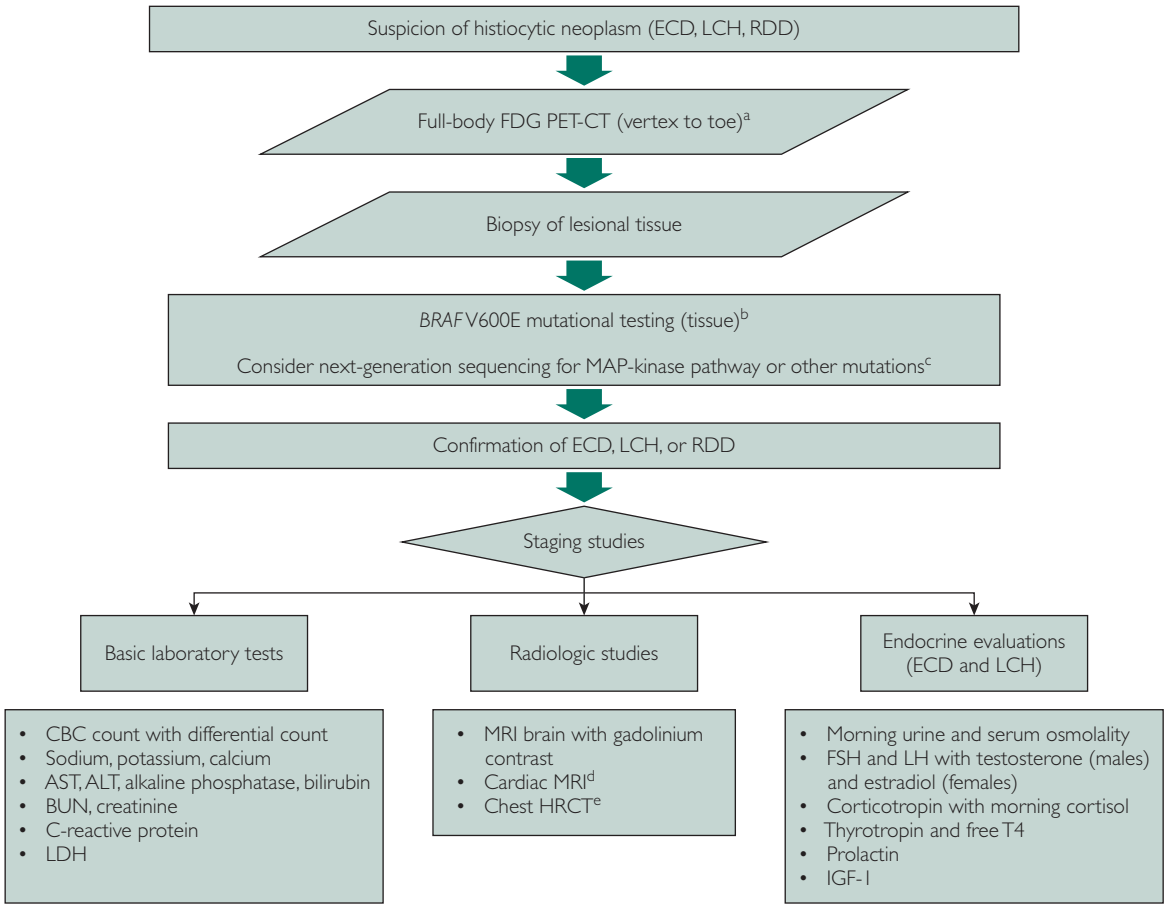


FIGURE 4. Suggested algorithm for the diagnosis and initial evaluation of patients with histiocytic neoplasms. ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood cell; ECD = Erdheim-Chester disease; FDG PET-CT = ^{18}F-fluorodeoxyglucose positron emission tomography–computed tomography; FSH = follicle-stimulating hormone; HRCT = high-resolution computed tomography; IGF-1 = insulinlike growth factor-1; LCH = Langerhans cell histiocytosis; LDH = lactate dehydrogenase; LH = luteinizing hormone; MAP = mitogen-activated protein; MRI = magnetic resonance imaging; RDD = Rosai-Dorfman disease; T4 = thyroxine. [a]FDG PET-CT may help in determining a safe and high-yield biopsy site. Some patients would have already undergone other imaging studies, which may be sufficient to guide a biopsy and establish a diagnosis. For those patients, FDG PET-CT may be considered clinically as a staging test. [b]Performed by immunohistochemical (IHC) analysis, polymerase chain reaction, or next-generation target capture sequencing. Confirm negative IHC analysis findings by at least 1 other molecular method. [c]Molecular profiling may aid in diagnosis in ambiguous cases, as well as identifying targets for treatment. [d]In ECD only. [e]Pulmonary LCH.

endocrine glands as well, which is more common than LCH.[55,60] Sonographic evidence of testicular infiltration can be seen in up to 30% of males but does not always correlate with testosterone levels or sperm count.[55] In our experience, testicular infiltration in patients with ECD may be seen due to concomitant RDD. Adrenal infiltration is also frequent and seen in 20% to 40% of patients, most commonly bilateral.[61] Of patients with radiographic adrenal infiltration, less than 20% develop primary adrenal insufficiency.[55,62] Thyroid involvement may present as an enlarging mass. The prevalence of primary hypothyroidism varies from 10% to 33%,[55,63] although it is unclear what percentage of hypofunction is related to histiocytosis itself.[55,62] Ovarian infiltration is extremely rare.[64] Endocrine abnormalities may be permanent, even with treatment of the disease.

Similar to ECD, the most common permanent endocrinopathy in LCH is DI, which is

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present in 20% to 30% of patients.[22,60] Diabetes insipidus can either be present before the diagnosis or manifest many years later.[58] The risk of developing DI is greater in patients with multisystem disease.[22] Anterior pituitary deficiencies typically correlate with DI and can occur years after LCH diagnosis.[65] Reports from small cohorts have shown that of patients with LCH and DI, 70% to 90% develop a concomitant anterior pituitary hormone deficit within 5 years, the most common being growth hormone deficiency (40%-67%), followed by gonadotropin deficiency (33%-58%), whereas corticotropin and thyrotropin deficiencies are less frequent (11%-30%).[58,59] The prolactin level is elevated in approximately 20% of patients.[58,59] Less than 50% of patients with hypopituitarism have abnormal imaging findings; conversely, almost all patients with abnormal imaging findings have pituitary hormonal deficiencies.[66] Similar to ECD, anterior and posterior hormone deficits are generally permanent and do not improve or resolve, even when LCH is successfully treated.[58] Involvement of other endocrine glands is rare in LCH and more frequent in the context of multisystem disease. Glands reported to be affected include the thyroid, parathyroids, ovaries, and adrenals.[60,66]

Endocrine manifestations are very infrequent in patients with RDD.[32,52,67,68] Very few cases of thyroid, testicular, and adrenal infiltration or encasement have been reported, and some of these represented local extension from adjacent lymph nodes (LNs).[30] In our experience, most patients with testicular RDD had concomitant ECD.[69]

Respiratory

Respiratory system involvement may manifest in up to half of the patients with ECD.[10] Unlike pulmonary LCH, there is no reported association with cigarette smoking. Common findings on chest CT include mediastinal infiltration, pleural thickening/effusions, and, less commonly, pulmonary parenchymal abnormalities (interlobular septal thickening, multifocal ground-glass opacities, nodules, or cysts). Pulmonary function abnormalities are commonly present in those with pulmonary involvement, although the pattern of abnormality varies. Histopathologic confirmation of ECD is usually made by biopsy from nonpulmonary sites. If lung tissue is required for diagnostic clarification, a surgical or bronchoscopic lung biopsy is generally needed, as percutaneous biopsies may have low diagnostic yield. Also, ECD may involve sinuses, leading to maxillary sinus wall thickening in up to 50% of patients.[13]

Pulmonary LCH is the most common histiocytic disorder of the lungs. More than 90% of adults with pulmonary LCH are active or former smokers.[70] Approximately one-third of patients are asymptomatic when diagnosed; the remaining two-thirds present with cough or dyspnea on exertion.[70] Constitutional symptoms occur in up to 20% of patients. Lung examination findings may be normal or demonstrate signs of airflow limitation. Findings on chest radiography are frequently abnormal, although nonspecific (eg, nodular or reticulonodular opacities bilaterally). High-resolution CT of the chest should be performed in any patient suspected of having pulmonary LCH. Small nodules measuring several millimeters to 2 cm—some with central cavitation—are often observed in the early stages.[71] In more advanced disease, nodules are less commonly seen and cysts predominate. Pulmonary function testing may reveal a reduction in diffusing capacity (observed in up to two-thirds of patients at the time of diagnosis) together with changes of either obstructive, restrictive, or mixed physiologic abnormalities.[70] However, spirometry and lung volumes may be completely normal, particularly in the early stages of disease. Bronchoscopic lung biopsy is associated with a diagnostic yield of up to 50%.[72] However, a surgical lung biopsy may be necessary if bronchoscopic biopsy is nondiagnostic. At the time of diagnosis, all patients should undergo echocardiographic assessment to screen for pulmonary hypertension. Right-sided heart catheterization and vasoreactivity testing should be considered in selected patients with echocardiographically demonstrated pulmonary hypertension to assess its severity and aid with further management.[73]

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Pulmonary involvement is seen in up to 20% of patients with RDD and may present as cystic change, interstitial lung disease, focal pulmonary infiltrate/nodule, or airway disease on imaging.[74] There is no reported association with cigarette smoking. In addition, sinus involvement can be seen occasionally as well, with maxillary sinus wall thickening similar to that seen with ECD.[31]

Dermatologic

Erdheim-Chester disease can affect the skin in up to 30% of patients. Half of these patients have cutaneous involvement at diagnosis. Typically, skin lesions are yellow-brown or xanthomatous papulonodules and indurated plaques ranging from a few millimeters to 1.5 cm in diameter.[75] The most common location is around the eyes as xanthelasma-like lesions, but the face, neck, and inframammary, axillary, and inguinal folds can also be affected.[76] Some patients report pruritus.

In LCH, cutaneous manifestations may occur as an erythematous papular rash located in the groin or on the abdomen, chest, or back. Scalp involvement may be misdiagnosed as seborrheic dermatitis. Other manifestations include subcutaneous nodules without epidermal changes. Xanthomatous lesions may be seen as red to purple nodules with a yellowish hue. Intraoral nodules, desquamative gingivitis, mucosal ulcers, and premature loss of primary dentition can be seen as well.[77]

Rosai-Dorfman disease involving the skin and subcutaneous tissue can be seen in a large proportion of patients (50%).[31] Solitary or multiple red-to-brown macules or papules or xanthomatous papules, nodules, and plaques usually around the orbits (eyelids) or malar region can be seen. Panniculitis (tender subcutaneous nodules) and isolated cutaneous involvement have been reported as well.[78]

Cardiac

Cardiac involvement is most commonly noted in ECD, less frequently in RDD, and almost never in LCH. Owing to a lack of systematic evaluation of cardiac involvement in patients with histiocytic neoplasms, reports on the frequency and location of abnormalities are incomplete. Among series in which thoracic imaging with CT or MRI was performed, 40% to 70% of patients with ECD had abnormal cardiac findings.[79-81] Although ECD can involve any cardiac layer, the most frequent finding is pericardial infiltration and effusion, which can be observed in up to 42% of patients.[79] Rarely, massive pericardial effusion complicated by cardiac tamponade may occur.[13,82] Myocardial infiltration is detected in more than one-third of patients, with the most common and characteristic findings of right atrial pseudotumor (30%-37%) followed by infiltration of the atrioventricular sulcus (19%).[13,79,81,82] The electrophysiologic effect of such involvement has not been systematically evaluated, but atrioventricular blocks requiring pacemaker insertion have been described.[79] Malignant arrhythmias have not been reported. Endocardial disease resulting in valvular dysfunction is less common; however, symptomatic aortic and mitral valve abnormalities have been described.[82] Cardiac involvement in ECD portends a poor prognosis, particularly if resulting in symptomatic heart failure.[82]

Cardiac lesions are exceedingly rare in LCH and if present should raise suspicion for an ECD/LCH overlap.[83] Cardiac involvement in RDD is rare but has been reported in 17 patients with infiltration of the atria, interatrial septum, left ventricle, and pericardium.[84] Classical symptoms of RDD are present in a minority of such patients, and, therefore, a high index of suspicion and histologic confirmation are required. In our own cohort, cardiac involvement was seen in less than 5% of patients.[31]

Arterial

Arterial involvement in histiocytic neoplasms rarely causes symptoms that lead to diagnosis.[85,86] Nevertheless, periarterial fibrosis of the thoracic or abdominal aorta is notably present in 56% to 85% of patients with ECD, with sheathing of the entire thoraco-abdominal aorta (ie, "coated aorta") in 23% to 30%.[13,80,82,87] The periarterial

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fibrosis is the result of histiocytic infiltration into the adventitia.[82,88,89] Although the characteristics and distribution of arterial lesions can vary, circumferential thickening is most commonly described. The perivascular tropism in ECD is not limited to the aorta. Indeed, periarterial thickening has been reported in up to 60% of supra-aortic trunk branches.[80] In addition, periarterial fibrosis of the visceral arteries has also been described in the superior mesenteric, celiac, and renal arteries.[82,87] Although involvement of the main aortic branch vessels generally has limited clinical consequence, mesenteric vessel disease has led to bowel ischemia in a minority of patients.[12,13] Renal artery stenosis from either isolated renal artery fibrosis or extension from periadventitial thickening of the abdominal aorta can result in resistant hypertension, which improves with endovascular stenting.[13,82] Periarterial thickening of the coronary arteries has been reported in as many as 55% of patients with ECD evaluated with thoracic CT angiography[80]; however, clinically significant stenosis requiring intervention or resulting in myocardial infarction seems uncommon.[80,81,88,90]

Direct lesional infiltration of arterial structures is not a characteristic observed in LCH, although envelopment of regional arterial structures due to tumoral expansion has been reported.[91] Arterial infiltration in extranodal RDD is considered exceptionally rare. Nevertheless, reports of extranodal RDD involving the carotid sheath and pulmonary artery have been described.[92-94]

Retroperitoneum, Including Kidneys

Histiocytic infiltration of the retroperitoneal space is frequently observed in ECD. By CT, this is seen as a diffuse bilateral infiltrative perinephric soft tissue thickening with a stellate pattern, the so-called hairy kidney, which is highly suggestive of ECD and present in 50% to 68% of patients.[95,96] Most retroperitoneal infiltrates are asymptomatic. However, extension of the mass either to the renal sinus or involving the middle to distal ureters may lead to hydronephrosis, ultimately requiring ureteral stenting.[95-97] Perinephric infiltrates may further extend into the adrenal fossa, resulting in faint nodularity to bulky masses, present in up to 32% of patients.[96,98]

Perinephric involvement of LCH is unusual in adults and has not been reported. Destructive interstitial nephritis[99] and membranous nephropathy have been associated with lesional tissue infiltration from LCH and require renal biopsy to confirm.[100] Perinephric infiltrate similar to ECD has been described in RDD but is much less common. The more common features observed with renal involvement of extranodal RDD include renal hilar masses, subcapsular hypodense infiltration, or renal cortical hypodense nodules.[101,102] Massive retroperitoneal adenopathy resulting in envelopment of the kidneys or ureters can lead to postrenal obstruction.[30] Although postobstructive uropathy is the most common cause of renal insufficiency in patients with histiocytic neoplasms, renal parenchymal disease must also be considered if proteinuria or hematuria is present, or if renal function fails to improve with ureteral stenting.

Reticuloendothelial and Hematopoietic System

The involvement of the reticuloendothelial system varies widely by the end organ involved as well as the disease. Liver and spleen involvement is uncommon in all three histiocytic disorders. In contrast, LN involvement occurs quite frequently in RDD but is quite uncommon in ECD and LCH.[13,22,31]

In a retrospective review of 45 patients with ECD, 11% each had liver and spleen involvement.[103] Langerhans cell histiocytosis involvement of the liver or spleen is uncommon (10%-15% each), and the prognosis is similar to that of those with pulmonary LCH.[22] In RDD, 27 of 157 patients (17%) studied had liver abnormalities, with the most common manifestation being hepatomegaly.[30] Of these, 4 patients had biopsy-proven involvement of the liver with RDD. Similarly, 15% of patients had spleen involvement clinically manifested as mild splenomegaly.[30] The presentation of liver

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involvement varies widely from incidental finding to jaundice, hepatomegaly, cyst- or mass-like lesions, ascites, or edema.

Involvement of the LNs in ECD is reported but quite uncommon.[86,104] On review of patients with ECD seen at Mayo Clinic, 4% of patients presented with lymphadenopathy, 1 of which had a biopsy-proven disease (unpublished data). Langerhans cell histiocytosis involving the LN alone is rare and may be observed or require localized therapies.[105] Involvement of the LNs as a part of multisystem LCH is seen in approximately 5% to 10% of patients and is thought to represent a higher risk of disease.[11,22] In contrast, lymphadenopathy is notably common in RDD and is referred to as *sinus histiocytosis with massive lymphadenopathy*. Although historically considered to be the most common manifestation, lymphadenopathy was seen in only one-third of our patients.[31] One of the frequent clinical presentations is painless lymphadenopathy involving cervical, axillary, or abdominal regions accompanied by B symptoms, but a few patients may have painful or tender LNs.[30] On PET-CT, LNs harboring RDD tend to have the most uptake centrally, with a photopenic halo.[106]

There are few data on bone marrow involvement in adults with histiocytic neoplasms. Bone marrow biopsy is not routinely performed in histiocytic neoplasms and is usually only undertaken to evaluate patients with abnormalities in peripheral cell counts, such as monocytosis, unexplained anemia, or thrombocytosis. In a recent report, patients with ECD or mixed LCH/ECD had a high prevalence of concomitant myeloid neoplasms (10%), specifically myeloproliferative neoplasm, myelodysplastic syndrome, or mixed myelodysplastic/myeloproliferative overlap syndrome, including chronic myelomonocytic leukemia.[107] In our experience, the prevalence of myeloid neoplasms is lower in patients with ECD (4%), although still higher than would be expected in the general population.[108] Approximately 30% of patients who underwent a bone marrow biopsy for abnormal peripheral blood counts were found to have ECD involvement in the marrow. Langerhans cell histiocytosis involving the bone marrow in adults had been reported, although its exact frequency is unclear.[109] In RDD, this percentage was low as well (6%).[31] We recommend a bone marrow evaluation in patients with unexplained peripheral blood cell abnormalities, especially monocytosis, thrombocytosis, or anemia.

HISTOPATHOLOGIC FEATURES AND TISSUE DIAGNOSIS

Pathologic diagnosis and classification of histiocytic neoplasms is challenging owing to the rarity of the diseases and the relatively nonspecific histologic findings. Furthermore, the neoplastic cells in ECD, LCH, and RDD are often sparsely distributed in the affected organ and are surrounded by varying degrees of fibrosis and inflammatory cells. Alerting the pathologist to the clinical suspicion of a histiocytic neoplasm is often crucial to its recognition. The diagnosis may require multiple biopsies, and targeting of anatomical sites with the greatest diagnostic yield is important. Although bone lesions are often the first identified site of disease, analysis of bone specimens is often limited by crush artifact and the decalcification process. Critical ancillary studies, including immunohistochemical (IHC) analysis and genetic testing for *BRAF* V600E, often give false-negative results on decalcified tissues. Hence, if a bone biopsy is performed, it is important to take additional cores to be processed without decalcification or pursuing decalcification using an EDTA-based method to enable molecular analysis.

Erdheim-Chester disease is characterized by collections of foamy histiocytes and rare Touton giant cells in a background of fibrosis.[1,110,111] Lymphoplasmacytic infiltrates may be present but are generally sparse. The histiocytes in ECD show similarly positive IHC markers as that of reactive histiocytes, except for those in which *BRAF* V600E mutation can be demonstrated (Table 1).[112] In our experience, classic histopathologic features of foamy histiocytes are not always present in the lesional tissue and instead may demonstrate nonspecific inflammation and fibrosis. In such cases, a

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diagnosis of ECD is often established using characteristic clinical or radiographic features or the presence of MAPK/ERK and phosphatidylinositol-3-kinase/protein kinase B (PI3K/AKT) pathway mutations.

Lesions of LCH are typically more cellular than those of ECD, and the neoplastic cells often show more overt cytologic atypia. Compared with reactive Langerhans cells, the cells of LCH may have nuclei that are slightly enlarged, with delicate nuclear grooves and less condensed chromatin.[11] Intermixed eosinophils are commonly present and often numerous. Fibrosis may be present, usually minimal in soft tissues but more pronounced in bone lesions. Langerhans cell histiocytosis involves LNs in a distinct sinus pattern, which distinguishes it from the paracortical distribution of reactive Langerhans cells seen in lymphadenopathy due to inflammatory skin conditions.[113] By IHC analysis, LCH shows a phenotype consistent with Langerhans cell differentiation, with expression of S100, CD1a, and Langerin. *BRAF* V600E mutation may also be demonstrated by IHC analysis.[114]

Compared with ECD and LCH, RDD infiltrates often show a more inflammatory background with numerous plasma cells and may also include lymphoid follicle formation and neutrophilic infiltrates.[9] The nuclei of the histiocytes are enlarged, with open chromatin and distinct centrally placed nucleoli. These histiocytes display emperipolesis, with engulfment of intact inflammatory cells within their cytoplasm. Fibrosis may be prominent, particularly in meningeal or paraspinal lesions. When involving LNs, the cells markedly distend the sinuses. The phenotype includes histiocytic markers, and there is also expression of S100.[9]

When a histiocytic neoplasm is suspected, immunohistochemical stains may be useful in the diagnosis and classification. The recommended panel includes CD163 or CD68, S100, CD1a, Langerin, and factor XIIIa.[1] Additional stains may be useful to exclude other entities, including systemic IgG4-related disease (IgG, IgG4), low-grade B-cell lymphoma (CD20, light chains), infection, fat necrosis, and idiopathic retroperitoneal fibrosis. In addition, for ECD and LCH, IHC analysis of paraffin sections using the *BRAF* V600E–mutant specific antibody has high specificity, although more sensitive testing, such as pyrosequencing or digital droplet polymerase chain reaction, may be more helpful in cases with equivocal or negative IHC testing.[114,115] The expected phenotypic profiles are outlined in Table 1.

WHEN TO SUSPECT HISTIOCYTIC NEOPLASMS

The varied clinical manifestations of histiocytic neoplasms make it challenging to ascertain a set of pathognomonic features. Most patients present with nonspecific signs and symptoms to their primary care providers and at times are referred to various subspecialists based on their symptoms. Unless these patients have abnormalities in the peripheral blood cell counts, which rarely occur in histiocytic neoplasms, they are not referred to hematology before diagnosis. In other scenarios, the histopathologic review of tissue specimens is suspicious for, but not classic for, a particular histiocytic neoplasm. This leads to a delay in diagnosis and institution of treatment in a substantial proportion of patients.

The earliest clinical cues that should raise suspicion for ECD and LCH are central DI and bony pain in the absence of other etiologies.[13,22] Of patients with apparently idiopathic central DI, up to 5% to 10% may be due to LCH or ECD.[116] However, "classic" instances are less common, and often a combination of clinical, radiologic, and histopathologic features is needed in light of one another to establish a diagnosis. This is especially true for ECD, where the histopathologic findings are often nondiagnostic due to abundant fibrosis and inflammatory infiltrate. The pathognomonic radiographic finding of ECD is metadiaphyseal osteosclerosis around the knees, and it can be elicited on vertex-to-toes (full-body) PET-CT or technetium-99m bone scintigraphy, although we prefer the former due to the ability to simultaneously evaluate for other

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organ involvement.[13] Other findings suggestive of ECD are infiltrative perinephric soft tissue thickening ("hairy kidneys") and smooth soft tissue thickening of the aortic adventitia ("coated aorta").[13]

In LCH, aggressive cortically based lytic bone lesions can be suggestive of the diagnosis. In cases with pulmonary involvement, the characteristic feature is upper lobe–predominant nodular cystic lesions seen in a smoker. Although RDD was historically described as massive neck lymphadenopathy, in our experience it presents with nonmassively enlarged (1-2 cm) LNs or subcutaneous lesions in adults.[31] Rosai-Dorfman disease can also be associated with autoimmune disorders such as systemic lupus erythematosus and malignancies such as lymphoma, which can serve as additional clues to aid in its diagnosis.[117,118] Key features suggestive of histiocytic neoplasms and prompting further evaluation are listed in Table 2.

INITIAL EVALUATION AND DIAGNOSTIC TESTS

All patients with suspected histiocytic neoplasms warrant baseline peripheral blood and imaging studies, which can aid in diagnosis and help ascertain the extent of disease (Figure 4). All of these neoplasms are FDG PET avid, which is our modality of choice to evaluate organ involvement. Because these may involve the lower extremities, we recommend the full-body (vertex-to-toes) PET-CT protocol instead of the conventional skull base–to-thigh protocol. Sometimes a focused evaluation using CT, MRI, or both may be necessary depending on patient symptoms. In addition, we recommend pursuing brain MRI due to high rates of CNS, dural, and orbital involvement, which may be asymptomatic, especially in patients with ECD and LCH. In patients with RDD, head MRI may be considered, especially for better evaluation of sinus and orbital disease compared with PET-CT. In patients with suspected ECD, cardiac MRI is recommended for capturing lesions that would otherwise be missed. In addition, we recommend comprehensive evaluation for endocrinopathies because imaging studies are not sensitive enough. Abnormalities in peripheral blood counts may also suggest the presence of a concomitant myeloid malignancy, which warrants a bone marrow biopsy.

Due to the challenges associated with histopathologic diagnosis of these neoplasms, we also recommend histopathologic reevaluation of ambiguous cases at centers with expertise in these neoplasms, especially those with atypical histiocytic infiltrates in the appropriate clinical context. Note that instances of mixed histiocytosis occur as well, with features of overlap between ECD and either LCH or RDD. The cases with mixed ECD/LCH are found to have a higher frequency of *BRAF* V600E mutations in the LCH (69%) and ECD (82%) lesions compared with that reported for either entity alone (50%-60%).[119] Erdheim-Chester disease may also co-occur with RDD, which mostly occurs in males, is almost always extranodal, frequently involves the testes, and most commonly is driven by *MAP2K1* mutation.[69] In addition, the presence of a *BRAF* V600 mutation in the tissue specimen nearly rules out RDD. Hence, in patients with nonclassic phenotypes or unclear histopathologic features, we recommend pursuing molecular profiling using target capture next-generation sequencing for MAPK/ERK and PI3K/AKT pathway gene mutations because the presence of such mutations can

TABLE 2. Features Suspicious for Histiocytic Neoplasms

Major features
1. Metadiaphyseal osteosclerosis of the femur, tibia, or fibula
2. Idiopathic central diabetes insipidus
3. Atypical histiocytic infiltrate ($CD68/CD163^{+}$) on tissue biopsy
Other features (combined with any major feature)
1. Dense retroperitoneal soft tissue proliferation "hairy kidney"
2. Medium to large vessel soft tissue "coating"
3. Upper lobe–predominant nodular cystic lung lesions in a smoker
4. Punched-out lytic osseous lesions, often involving flat bones (skull, sternum, ribs, pelvis)

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help in establishing the diagnosis of a histiocytic neoplasm regardless of the specific histology. Furthermore, the presence of these mutations also aids in subsequent treatment using targeted agents.[8,120,121]

CONCLUSION

In summary, these guidelines are based on review of existing literature and our own experience. Hence, they are likely subject to change as new data emerge. We hope that the comprehensive clinical phenotype descriptions, in conjunction with the evaluation and workup guidelines, help in raising awareness of these disorders and lead to correct and early diagnosis. Because we now have targeted therapies for these histiocytic neoplasms on the horizon, an accurate and expedited diagnosis of these rare neoplasms will hopefully allow for more timely treatment with better outcomes.

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Abbreviations and Acronyms: **ALT** = alanine aminotransferase; **AST** = aspartate aminotransferase; **BUN** = blood urea nitrogen; **CBC** = complete blood cell; **CNS** = central nervous system; **CT** = computed tomography; **DI** = diabetes insipidus; **ECD** = Erdheim-Chester disease; **FDG** = ^{18}F-fluorodeoxyglucose; **FNA** = fine-needle aspiration; **FSH** = follicle-stimulating hormone; **H&E** = hematoxylin and eosin; **HRCT** = high-resolution computed tomography; **IGF-1** = insulinlike growth factor-1; **IHC** = immunohistochemical; **LCH** = Langerhans cell histiocytosis; **LDH** = lactate dehydrogenase; **LH** = luteinizing hormone; **LN** = lymph node; **MAP** = mitogen-activated protein; **MAPK/ERK** = mitogen-activated protein kinase/extracellular signal–regulated kinase; **MRI** = magnetic resonance imaging; **PET-CT** = positron emission tomography–computed tomography; **PI3K/AKT** = phosphatidylinositol-3-kinase/protein kinase B; **RDD** = Rosai-Dorfman disease; **T4** = thyroxine

Affiliations (Continued from the first page of this article.): and Nutrition (C.J.D.-P., M.D.H.), Department of Laboratory Medicine and Pathology (A.R., K.L.R.), and Department of Dermatology (J.C.S.V.), Mayo Clinic, Rochester, MN. Dr Goyal is now with the Division of Hematology-Oncology, University of Alabama at Birmingham.

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Correspondence: Address to Ronald S. Go, MD, or Gaurav Goyal, MBBS, Division of Hematology, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (Go.Ronald@mayo.edu or ggoyal@uabmc.edu).

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