Supplemental Material

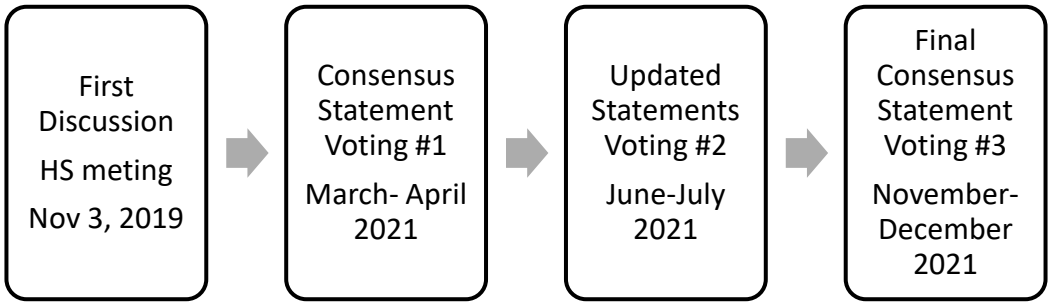
Supplemental Table 1. Composition of the consensus panel

The co-authors for the consensus document were selected based on the following criteria: a) Publication experience in the field of LCH in adults, or b) Clinical expertise in the field of histiocytosis and engagement in the Histiocyte Society meeting in November 2019.

Total members	18
Hematology/Oncology	6
Hematology/Molecular Biology	1
Pulmonology	2
Pathology	2
Radiology	2
Endocrinology	2
Immunology	1
Internal Medicine/Rheumatology	1
Neurology/Neuro-Oncology	1

Supplemental Appendix 1. Methods and Results

We utilized a modified Delphi approach with iterative multistage process to generate and vote on consensus statements. The conceptualization of the document and key statement areas was undertaken at the Histiocyte Society (HS) meeting on November 3, 2019. For review of pertinent evidence, an English language search of PubMed and Web of Science was conducted for LCH-related literature from January 1990 through September 2021. Based on the discussions, the document text and consensus statements were generated to be voted upon. For review of pertinent evidence, an English language search of PubMed and Web of Science was conducted for LCH-related literature from January 1990 through September 2021. We utilized a RedCap based survey to capture member votes as “agreement”, “disagreement”, and “not-qualified to answer”. After the first round of voting, statements were updated based on author comments, with reiterative voting conducted twice. The comments from dissenters were captured and presented in the table footnotes.



Diagnosis	**Consensus recommendation category and votes**
A biopsy of lesional tissue is recommended even in circumstances of highly suggestive clinical and imaging features to confirm LCH diagnosis and to establish BRAF or other MAPK-ERK pathway mutational status. Cases of pulmonary LCH (pLCH) with typical radiologic findings and clinical context are a reasonable exception, although a biopsy is encouraged in these cases as well.	A (17/17)
LCH should be considered in the presence of characteristic clinical/radiologic features (Table 3), even when histopathologic review is equivocal. Molecular analysis of tissue for BRAF and MAPK-ERK pathway mutations can be helpful in diagnosis of questionable lesions.[a]	B (17/18)
Baseline full-body (vertex-to-toes) FDG-PET/CT, including the distal extremities, is recommended to aid in diagnosis and define extent of disease.[b]	B (15/16)
Organ-specific imaging (CT, MRI) may be needed to further assess involved sites of disease based on initial imaging studies.	A (17/17)
MRI of the brain with gadolinium, with dedicated examination of the sella turcica, should be undertaken at diagnosis in cases with pituitary dysfunction or neurologic symptoms.	A (16/16)
In patients with suspected/confirmed pLCH, high-resolution CT scan (HRCT) of the	A (16/16)

chest should be performed.	
In patients with pulmonary LCH, a surgical lung biopsy may be necessary to confirm the diagnosis if bronchoscopic biopsy or other methods are non-diagnostic.	A (18/18)
All patients with pulmonary LCH should undergo pulmonary function testing (spirometry with lung volumes, diffusion capacity, and plethysmography) at the time of diagnosis.	A (15/15)
All patients with pulmonary LCH who are symptomatic or have abnormal diffusing capacity for carbon monoxide should undergo resting trans-thoracic echocardiogram to screen for pulmonary hypertension.	A (14/14)
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.	A (14/14)
MRCP (magnetic resonance cholangiopancreatography) or ERCP (endoscopic retrograde cholangiopancreatography) should be performed in cases with elevated serum cholestasis markers or sono-morphologically dilated bile ducts to evaluate for sclerosing cholangitis related to LCH	A (16/16)
For patients with suspected sclerosing cholangitis as a manifestation of LCH, early liver biopsy should be considered for histopathologic and mutational assessment.	A (16/16)
Laboratory studies to assess for liver insufficiency, cytopenias, markers of inflammation (C-reactive protein) should be performed at diagnosis.	A (16/16)
For patients with polyuria/polydipsia or involvement of pituitary/hypothalamus axis on cranial imaging, laboratory evaluation should be undertaken to rule out diabetes insipidus (DI) and anterior pituitary function	A (16/16)
Currently, there is no role for routine bone marrow biopsy in adult LCH. However, due to a high prevalence of concomitant and subsequent myeloid neoplasms in patients with LCH, bone marrow biopsy should be considered in the context of otherwise unexplained cytopenias or cytosis.	A (16/16)
All patients with LCH should undergo BRAF-V600E mutational testing to aid in diagnosis and treatment.	A (17/17)

Immunohistochemistry for VE1 may not be a sensitive or specific marker for BRAFV600E mutational analysis and should be confirmed with another molecular assay if feasible.[c]	B (13/14)
For BRAF-V600-wt LCH cases, next generation sequencing should be considered to assess for MAPK-ERK pathway mutations, especially in situations where the diagnosis is questionable or second-line treatment is needed.	A (17/17)
In the absence of sufficient tumor tissue, cell-free DNA analysis from peripheral blood can be utilized for assessment of BRAF-mutational status. However, the sensitivity of such assays may be variable.	A(17/17)
Treatment	
Unifocal LCH	
For unifocal LCH (except DI), observation or local therapies such as surgical excision, intralesional steroids, or radiation are recommended as first-line treatments.[d]	B (14/15)
For unifocal LCH involving specific sites (nervous system, liver, spleen, etc.), systemic treatment may be warranted.	A (16/16)
For unifocal LCH of pituitary/hypothalamus resulting in DI and anterior pituitary dysfunction, hormone replacement should be undertaken. The role of systemic therapy is unclear and may be considered in cases with symptoms that are recent-onset, or when a radiologic lesion is present.[e]	B (11/13)
Single-system pulmonary LCH	
Cessation of smoking, vaping, inhalation of marijuana or other substances is recommended as first-line therapy for single-system PLCH.	A (16/16)
Systemic therapy is appropriate for single-system PLCH in the presence of progressive disease (regardless of smoking status) or for stable disease with clinically significant respiratory symptoms or dysfunction.	A (16/16)
For patients who develop advanced single-system PLCH refractory to or ineligible for systemic treatments, lung transplantation should be considered.	A (16/16)

Multi-focal and multi-system LCH	
For multi-focal osseous LCH, suggested treatments are radiation therapy (<3 lesions safely amenable to radiation), bisphosphonates, or systemic chemotherapy.[f]	B (12/14)
For multi-focal cutaneous LCH, suggested treatments are topical therapy, oral low-dose weekly methotrexate, hydroxyurea, 6-MP, or IMiDs.[g]	B (12/13)
For multi-system LCH or extensive/refractory multi-focal single-system LCH, systemic chemotherapy agents such as cladribine, cytarabine, or vinblastine + prednisone are recommended.[h]	B (12/13)
For LCH involving the brain parenchyma, first-line treatment with chemotherapy with cladribine or cytarabine is recommended.	A (13/13)
For LCH refractory to first-line treatment or with end-organ dysfunction (e.g., neurologic impairment, sclerosing cholangitis), alternate conventional treatment or targeted therapies (BRAF- or MEK-inhibitors) may be used.	A (14/14)
Response assessment and monitoring	
The type and frequency of response assessments and follow-up examinations are variable and dependent on the degree of involvement with LCH (Table 7).	A (16/16)
For initially FDG PET avid LCH, it is recommended to repeat an FDG PET based imaging study for assessment of disease response after 2-3 months of initiation of therapy, with subsequent imaging frequency tailored individually based on specific clinical scenario.	A (15/15)

IMiDs: immunomodulators (thalidomide, lenalidomide); 6-MP: 6-mercaptopurine; CNS: central nervous system

[a]As with the first question LCH is with possible exception of lung and biliary tree, a pathological diagnosis. It is mandatory to have tissue (not just recommended) and I am not sure LCH should be considered unless pathologically confirmed.

[b]I do not think that PET-CT should be systematic, particularly in clinically localized disease.

[c]A properly optimized immunohistochemical test using the VE1 clone can provide a sensitive and specific marker for BRAF V600E mutation. Molecular genetic analysis for confirmation should be performed if the IHC result is equivocal or negative.

[d]We do not use radiation for localized LCH in France

[e]Tempted to agree but I think we need a trial for this - it would be great to give all idiopathic DI MRI and a MEK inhibitor

[f]We do not used radiation in this setting in France; I don't think hrdroxyurea could work on these patients low dose AraC should be considered.

[g]I do not endorse topical therapy. The other options are much better.

[h]Vinblastine and prednisone regimen has high failure rate and is more toxic in adults. Cladribine or cytarabine should be preferred.

Supplemental Appendix 2. Clinical and radiographic features of LCH in adults

Bones:

Lytic osseous lesions occur in 30-50% of all adults with LCH, manifesting as bone-limited or as a component of multisystem disease.[1,2] In up to 80% patients, these lesions remain isolated, historically known as 'eosinophilic granuloma', a lesion starting in the medullary cavity eventually eroding into the cortex.[3-5] The skull and dental sites are frequently affected, followed by axial and proximal appendicular skeleton, but any bony site can potentially be involved.[5,6] The frequencies of bone involvement include the jaw (8-30%), skull (21-28%), pelvis (12-22%), vertebrae (3-13%), rib (7-25%), and extremities (17%). Symptoms may vary from pain to local complications (e.g., cranial nerve dysfunction, radiculopathy, hearing loss, otitis media) due to growth involving adjacent tissue structures.[7] In some instances, LCH may involve the alveolar bone causing gingival recession and tooth loss with or without mandibular involvement.[8] Isolated lesions may resolve spontaneously or after biopsy, but may lead to bone destruction and deformity if not treated. 18F-fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (FDG-PET/CT) is a highly sensitive tool for bone lesion detection, and is superior to other imaging studies like CT and MRI.[9-11] We do not recommend technetium 99m-bone scintigraphy for detecting osseous lesions due to its low sensitivity.[6] On FDG-PET/CT, LCH bone lesions are lytic,

involve the cortex, and have a “punched-out” appearance. Although FDG-PET/CT is the recommended initial imaging modality for LCH, whole body MRI may be preferable in detecting small vertebral and skull lesions.[12]

Skin

Isolated skin involvement with LCH in adults is uncommon (5-10%), and tends to occur more commonly as part of multi-system disease (20-50%).[1,13] The most common presentation of cutaneous LCH is an erythematous papular rash with scaling and crusting, located on the chest, back, abdomen, limb, scalp or groin. Other less common manifestations include mucosal involvement of the perianal region, genitalia, or oral cavity. [14-16] At times, cutaneous and mucosal LCH are exquisitely painful and may present as non-healing wounds or ulcers. Xanthomatous lesions and subcutaneous nodules are rare and should raise concern for non-LCH. Compared with cutaneous LCH in children that frequently progresses to multi-system disease,[17] isolated skin LCH in adults tends to be more protracted, and in one study only 20% of adult patients developed disease elsewhere at 10 year follow up.[18]

Endocrine

LCH leads to permanent posterior and/or anterior pituitary hormonal deficiencies in a significant proportion of patients, which may not be associated with abnormal hypothalamo-pituitary imaging, as lesions may evolve or be subtle.[19-22] Diabetes insipidus is common, affecting 25% of all patients and may present before or years after the diagnosis of LCH.[23,24] Therefore, it is critical to consider LCH in the differential for idiopathic central diabetes insipidus to capture the diagnosis early. Anterior pituitary dysfunction is found in up to 20% of cases, and includes growth hormone, gonadotropin, thyroid-stimulating hormone, and adrenocorticotropic hormone deficiency in descending order.[20,25] A high proportion of patients with LCH and diabetes insipidus may develop anterior pituitary dysfunction eventually.[20,24,26] Decreased bone mineral density[21,27] and insulin resistance[28] have also been described

in a proportion of patients. While there are no prospective studies assessing their evolution with treatment of LCH, most endocrinopathies are not reversible despite systemic treatment and radiographic disease improvement, necessitating life-long replacement therapy.[24]

Nervous system and orbit

The frequency of nervous system involvement in adults with LCH is about 15-20%,[2] and may manifest as focal mass lesions in the pituitary stalk, followed by hypothalamus and pineal gland. Dura-based lesions occur either alone or by direction extension from the calvarium. Orbit involvement is very rare compared with ECD, although orbital extension from LCH of cavernous sinus has been reported.[29] Infiltration of the brain parenchyma can rarely occur, most often in the cerebellum or brainstem, leading to symptoms such as ataxia and dysarthia.[30,31] Gadolinium-enhanced MRI usually demonstrates abnormal enhancement of mass lesions.[32] FDG-PET/CT may show these lesions with variable levels of FDG uptake. [33] Neurodegenerative LCH, an entity defined initially in pediatric and adolescent patients, is rare in adult-onset LCH; it is characterized by progressive cerebellar syndrome and multi-domain neurologic decline.[32] We prefer the utilization of the terms “LCH-associated abnormal CNS imaging” (LACI) and “LCH-associated abnormal CNS symptoms” (LACS) for the radiographic and clinical manifestations of this entity, respectively. LACI has the MRI appearance of T2 hyperintense lesions and atrophy predominantly involving the posterior fossa.[32] Adult LACS can manifest as neuropsychological impairment and gait ataxia.[34] There can often be a delay of 10-20 years between LCH diagnosis and obvious neurocognitive impairment/diagnosis of LACI/LCAS, suggesting a need to be vigilant of this entity among adult survivors of pediatric-onset LCH.[34] Among survivors of pediatric LCH, LACS and LACI is mostly associated with central diabetes insipidus, but such a correlation has not been reported in adult-onset LCH.[34]

Pulmonary

PLCH can be seen in 40-50% of cases, mostly presents as single-system disease. Approximately two-thirds of patients with PLCH complain of non-specific respiratory symptoms (cough, dyspnea on exertion, chest pain, wheezing), while 10% may present as a pneumothorax.[35] Constitutional manifestations (fatigue, fever, night sweats and weight loss) are seen in 10-20% cases.[35] In a significant proportion of patients, the disease is discovered incidentally on chest imaging. When present, extrapulmonary lesions involve mainly the bones, pituitary stalk and rarely the skin.[35] Approximately 10% of patients with newly diagnosed PLCH have normal lung function parameters.[36] Decreased diffusing capacity for carbon monoxide (DLCO) is the most common abnormality (80-90%) in combination with changes of either obstructive, restrictive, or mixed physiologic abnormalities.[35] Blood gas levels at rest are normal in most cases but exercise capacity is frequently impaired, even in patients with mild dyspnea.[37]

Standard chest radiography is suggestive of PLCH when showing bilateral reticulonodular changes, predominating in the upper and middle fields, in which cysts may be visible. Lung high-resolution computed tomography (HRCT) may show nodular or cystic lesions in combination or in isolation as well as cavitary nodules and thick- and thin-walled cysts (Figure 1). In more advanced cases, lung cystic lesions of variable size predominate, and may coalesce in cysts of irregular shapes ("bizarre cysts"). These findings on HRCT are diagnostic of PLCH, especially in the context of smoking. Significant mediastinal lymph node enlargement is unusual and suggests an alternative diagnosis. Pulmonary artery enlargement is suggestive of pulmonary hypertension. In young adults who developed PLCH as teenagers, cystic lesions frequently predominate in the lung bases.[38] PLCH lung nodules can be hypermetabolic on FDG PET-CT, which does not allow differentiation from other malignant lesions. Thick-walled cysts may also demonstrate FDG uptake.[10,39] In the evaluation of adults with clinically isolated single-system PLCH, FDG-PET/CT is recommended in the presence of constitutional symptoms,

signs/symptoms suggestive of extra-thoracic disease, or clinical contexts where extra-thoracic involvement affects management (consideration of non-pulmonary biopsy site, classification of disease as unifocal or multifocal).

Bronchoscopy is macroscopically normal or shows smoking-related airway inflammation in PLCH. Bronchial mucosa biopsy specimens are not useful for the diagnosis but are helpful to rule out alternative diagnoses in atypical cases. Bronchoalveolar lavage (BAL) is rarely diagnostic of PLCH, but provides additional orientation by showing a marked predominance of alveolar macrophages, reflecting patients' daily tobacco consumption.[40] An increased percentage of CD1a+ cells (>5%) is highly suggestive of PLCH, but has a low sensitivity.[40]

Liver and spleen

Liver involvement can occur in 10-15% cases,[1] and is seen more commonly among patients with multisystem LCH.[41] LCH involvement of liver can occur in two forms- early stage disease with parenchymal infiltration by LCs (hepatomegaly, liver nodules, mild cholestasis, and elevated transaminases) or late stage sclerosing cholangitis-like disease with fibrosis of the bile ducts (severe cholestasis).[41] Some studies have suggested that liver involvement by LCH may be associated with a worse prognosis as compared with other forms of LCH.[13] This is especially true of the sclerosing cholangitis manifestation, which can quickly progress to cirrhosis and end-stage liver failure.[42] Magnetic resonance cholangiopancreatography may be normal or show irregularities of intrahepatic bile ducts, and is the recommended initial test (Figure 1).[42] Early biopsy of the liver may lead to confirmation of the diagnosis by means of showing CD1a positive LCs; however, in the later stages the biopsy may often yield fibrotic lesions with little to no histiocytic infiltration. Therefore, if a patient with known LCH develops biochemical and radiographic features of sclerosing cholangitis, it should be attributed to LCH

even with a negative biopsy.[43] Spleen involvement occurs in 10-15% of adult LCH patients, and may co-occur with liver disease.[13,30]

Bone marrow and lymph nodes

Bone marrow involvement can occur in LCH, but has not been systematically evaluated.[44] The presence of hematopoietic dysfunction in the form of leukopenia, anemia or thrombocytopenia may suggest involvement of the bone marrow by LCH or an underlying myeloid disorder like myelodysplastic syndrome, myeloproliferative disorder, or acute leukemia. LCH isolated to lymph nodes alone is uncommon and should be confirmed with extensive staging.[45] Involvement of lymph nodes as part of multisystem LCH may occur in 10-30% of patients.[2,13,46]

Other rare manifestations

Gastrointestinal involvement with LCH is rare, reported only as single case reports. Patients may present with diarrhea, abdominal discomfort, or an incidental polyp on colonoscopy conducted for unrelated reasons with otherwise normal radiologic studies. [47-49] Although the encasement of arterial structures due to regional tumor expansion has been reported,[50] cardiovascular involvement is exceedingly rare in LCH and if present, should raise suspicion for an LCH/ECD overlap.

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