National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Histiocytic Neoplasms

Version 1.2021 — March 1, 2021

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NCCN Guidelines Version 1.2021
Histiocytic Neoplasms

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Histiocytic Neoplasms

Clinical Trials: NCCN believes that the best management for any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

To find clinical trials online at NCCN Member Institutions, click here: nccn.org/clinical_trials/member_institutions.aspx.

NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise indicated.

See NCCN Categories of Evidence and Consensus.

NCCN Categories of Preference: All recommendations are considered appropriate.

See NCCN Categories of Preference.

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.

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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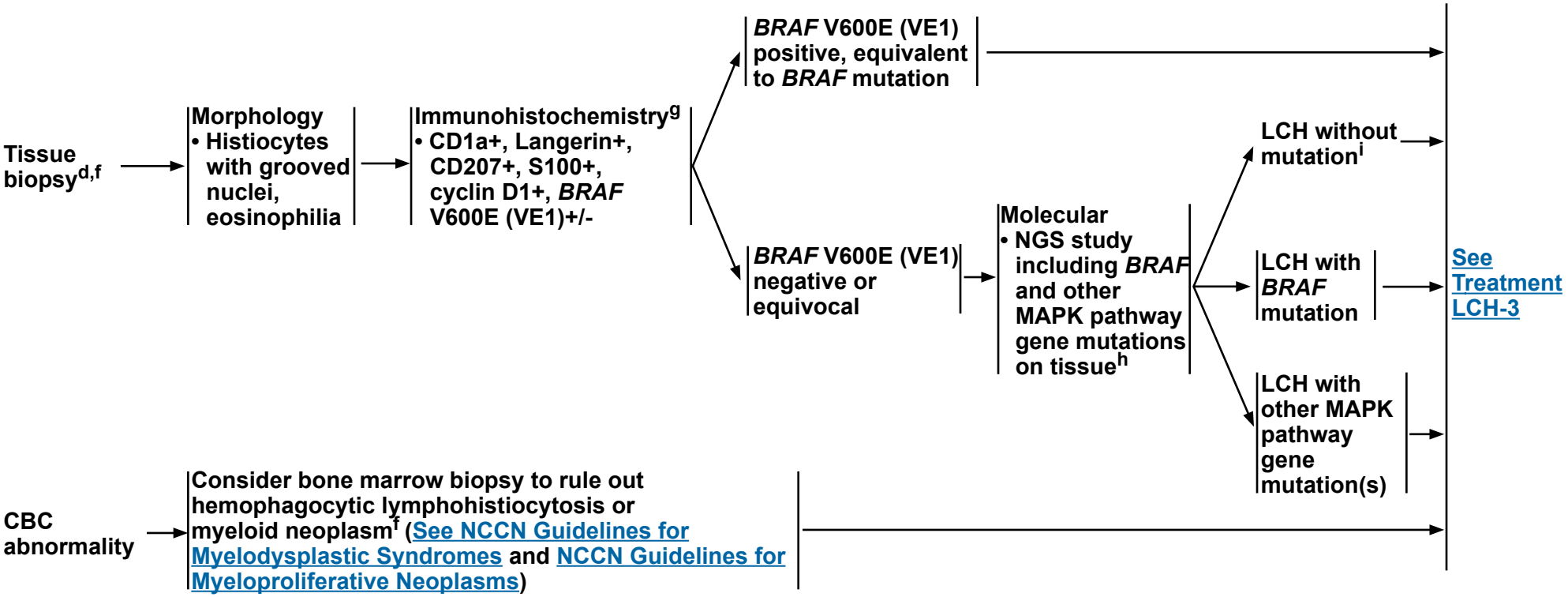
TISSUE BIOPSY ANALYSIS FOR LCH



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.

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NCCN Guidelines Version 1.2021
Langerhans Cell Histiocytosis

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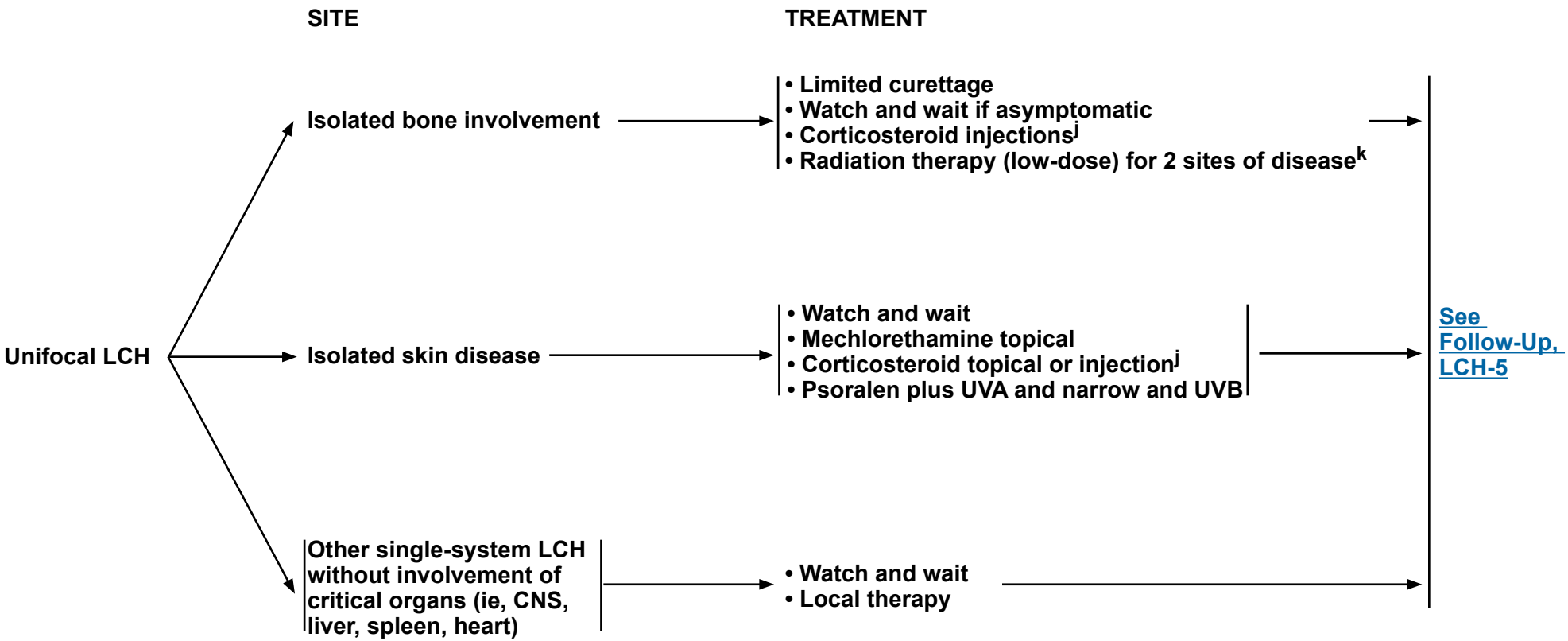

[j]Triamcinolone injection or equivalent corticosteroid.
[k]Use clinical judgment for 3 sites.

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Langerhans Cell Histiocytosis

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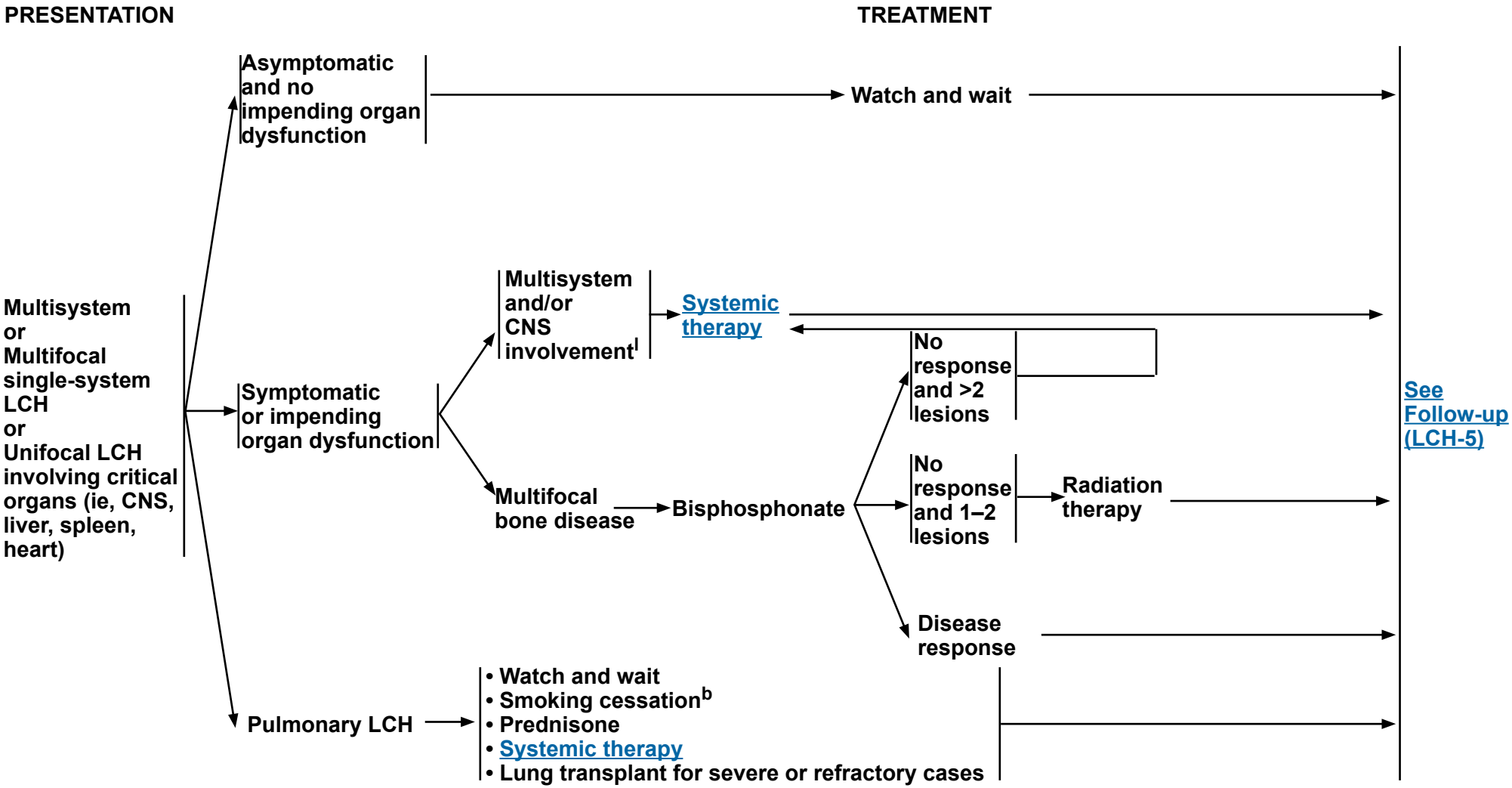

[b]Provide resources for smoking cessation. See NCCN Guidelines for Smoking Cessation.
[l]For neurodegenerative LCH, imaging changes precede clinical progression. Cognitive symptoms should be carefully monitored, and early treatment considered.

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FOLLOW-UP

Imaging of involved sites to evaluate treatment response (PET/CT [preferred], CT, or MRI)
- **After 2–3 cycles of systemic therapy and at completion**
- **After completion of surgical curettage**
- **After radiation therapy**

Surveillance
- **H&P and labs as clinically indicated**
- **Imaging: PET/CT (preferred), CT, or MRI**
  - **Every 3–6 months for the first 2 years post completion of treatment**
  - **>2 years: no more than annually**
  - **For asymptomatic patients with a single-site bone lesion, imaging surveillance can potentially end after year 1, with continued tracking of symptoms**
- **Pulmonary function testing for pulmonary LCH**
- **Bone marrow evaluation in the presence of cytopenias or other blood count abnormalities (to rule out associated myeloid neoplasm)**
- **Regular skin examination and ECG for patients treated with BRAF inhibitors[e]**
- **Monitor every 1–2 years for pituitary hormone abnormalities**

RELAPSED/ REFRACTORY DISEASE

→ **Systemic therapy**
- **If duration of response >1 year, consider same regimen; otherwise use a regimen not used for first-line**

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

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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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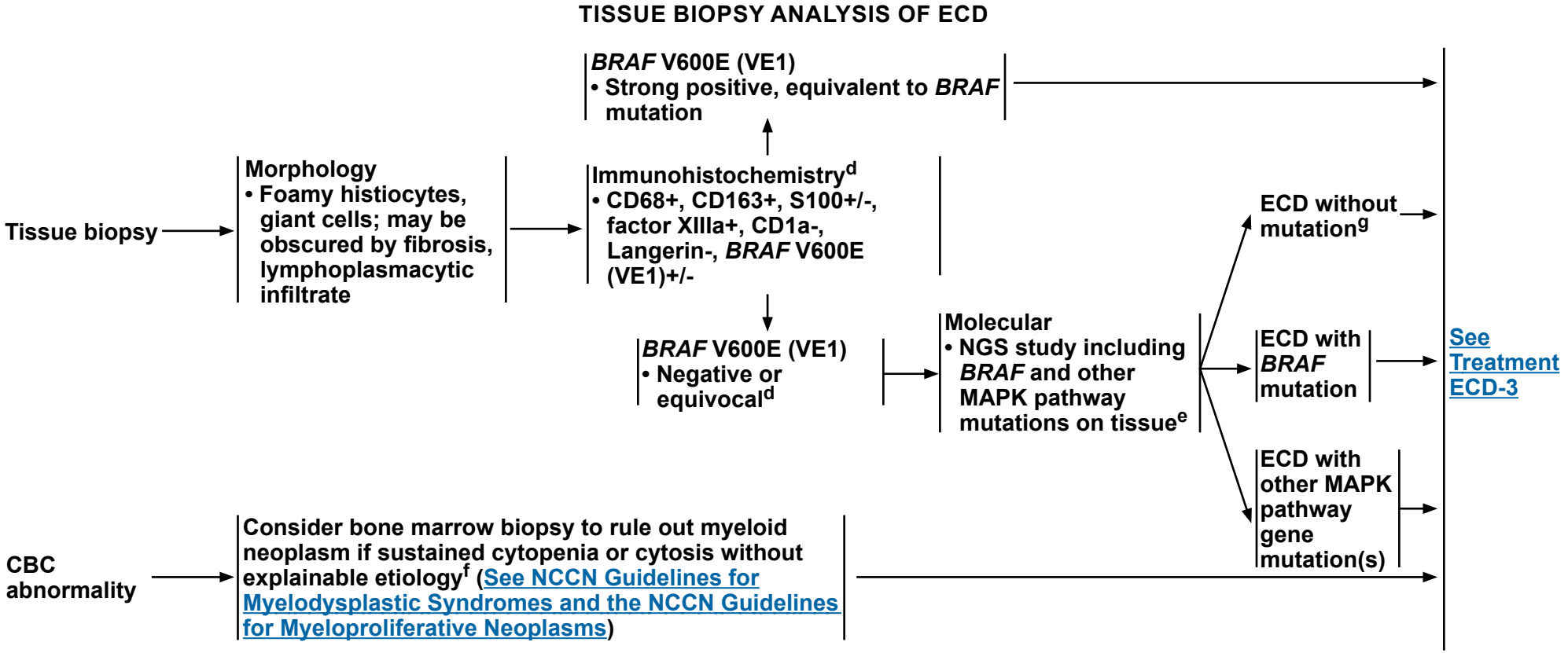

Immunophenotype key: +/-: positive or negative; +: positive; –: negative

[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.

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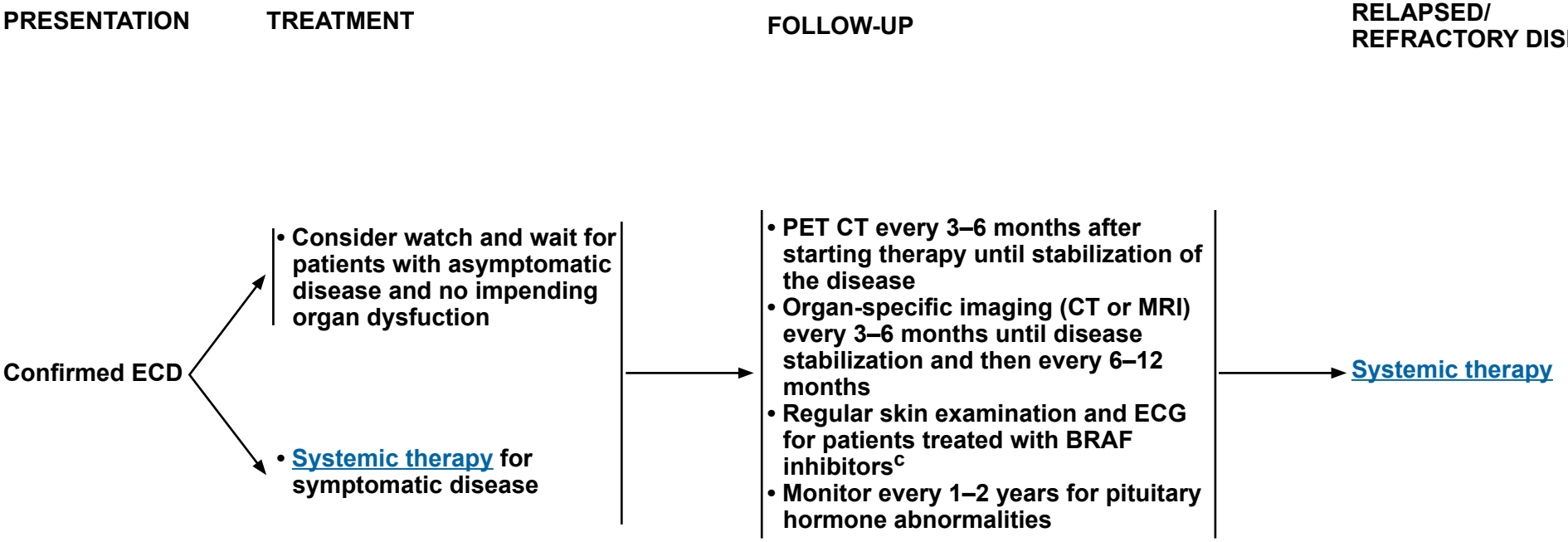
Erdheim-Chester Disease



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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.

See Treatment (RDD-3)

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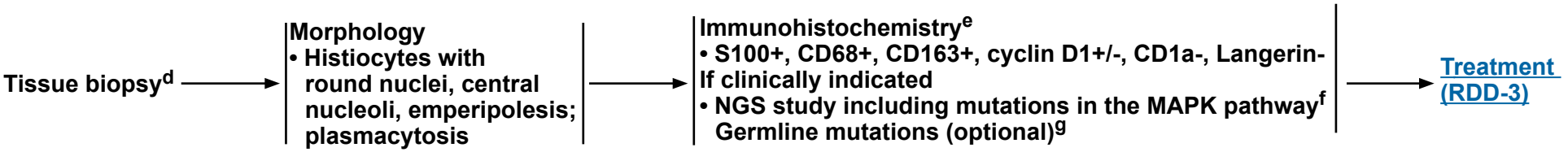
TISSUE BIOPSY ANALYSIS OF RDD



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.

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NCCN Guidelines Version 1.2021
Rosai-Dorfman Disease

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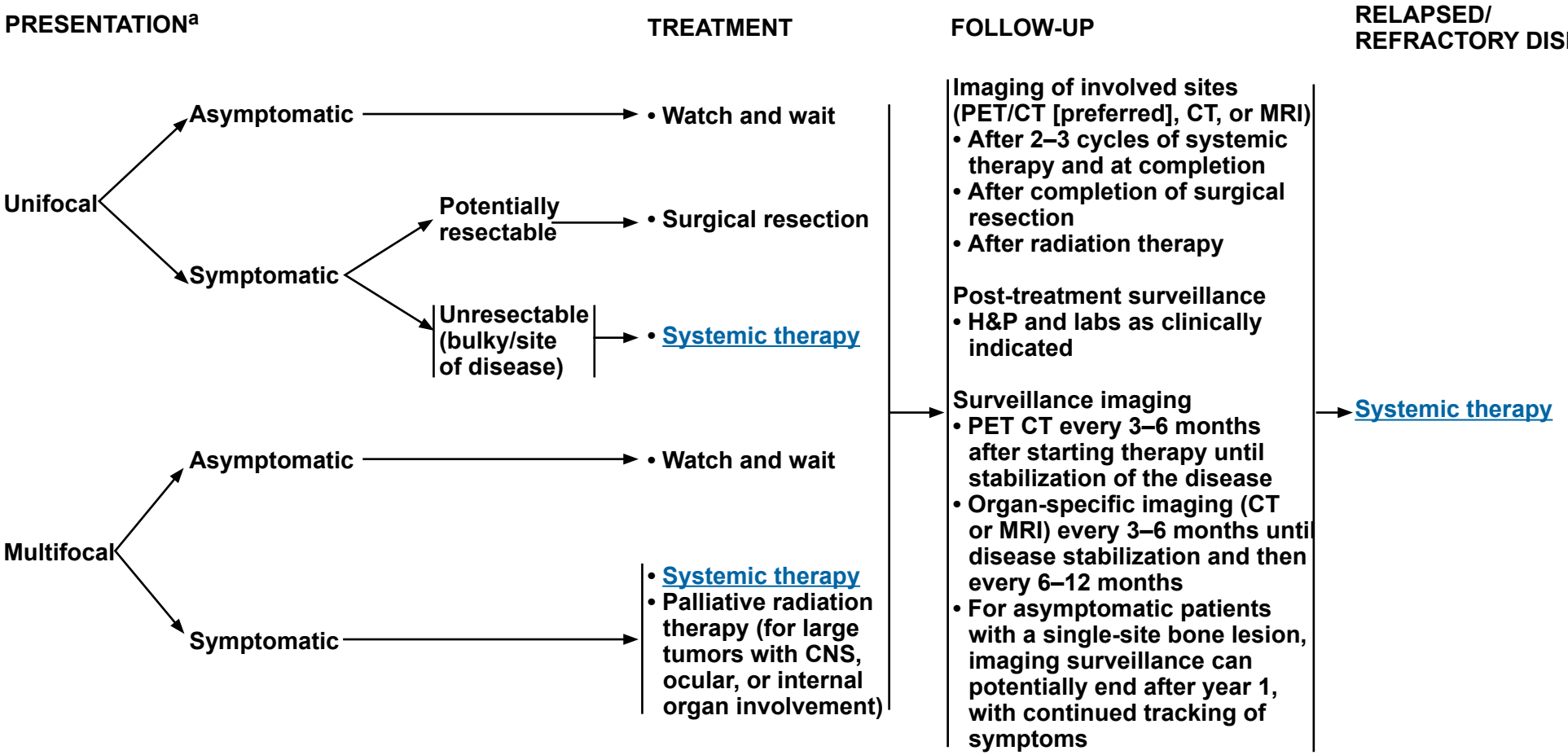

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PRINCIPLES OF PATHOLOGY

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 CD207 (Langerin).
- 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

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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, CD207/Langerin). 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

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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.

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Continued

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)	++	—	—
• CD207 (Langerin)(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.

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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.

Continued

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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.

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Continued

PRINCIPLES OF SYSTEMIC 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.

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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.

Continued

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NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

NCCN Categories of Preference	
Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

DISCUSSION
UNDER
DEVELOPMENT