Survivorship Issues in Adult Patients With Histiocytic Neoplasms

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ABSTRACT

Adult-onset histiocytoses (AOH), primarily Rosai-Dorfman disease (RDD), Erdheim-Chester Disease (ECD), and adult Langerhans cell histiocytosis (ALCH), are a group of related histiocytic neoplastic disorders featuring multisystemic manifestations. The disorders are largely incurable, and are essentially chronic neoplastic diseases with a variable prognosis. Prompt diagnosis and treatment is important to prevent debilitating and even life-threatening complications. Survivorship issues abound in AOH, due to their multisystemic manifestations and the sometimes recalcitrant chronic inflammation, which can lead to other debilitating complications such as fatigue, weakness, and pain. Because these disorders are rare, few healthcare professionals are proficient in their management; therefore the aim of these guidelines is to offer guidance on how to manage patients, and how to create survivorship care plans through the efforts of an interdisciplinary team.

J Natl Compr Canc Netw 2021;19(11):1312–1318
doi: 10.6004/jnccn.2021.7096

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Adult-onset histiocytoses (AOH), primarily Rosai-Dorfman disease (RDD), Erdheim-Chester Disease (ECD), and adult Langerhans cell histiocytosis (ALCH), are rare neoplastic disorders of activated histiocytes, key cells of the innate immune system that, when pathologically activated and proliferating, can create an uncontrolled inflammatory response. Dysregulated inflammation, in conjunction with tumor burden, contributes to end-organ damage, and potentially organ failure.[1,2] Severity of disease is broad, and some patients are only mildly affected, whereas others have multiple organ systems affected simultaneously, resulting in substantial functional loss and increased morbidity and mortality.[1,3,4] Moreover, some patients may be mildly affected but unexpectedly develop more serious complications, whereas others who are seriously affected may show dramatic improvement after treatment. This variability in the natural history of disease and response to therapy makes prognostication difficult and underscores the importance of providing diligent care and educating clinicians and patients about the manifestations of these rare disorders.

Survivorship Issues in AOH

Rarity of the Histiocytoses

Education is key. Because AOH are rare, it is likely that patients, family members, and even some medical providers will not be familiar with these disorders and their clinical implications. This is particularly important for medical providers, who are responsible for ordering diagnostic tests, managing symptoms, prescribing treatment, identifying complications, and marshalling resources to meet patients' needs. Incorrect initial diagnoses or prolonged diagnostic evaluations are common and may result in delayed treatment, increasing the risk of poorer outcomes.[2,5] Patient advocacy organizations such as the Histiocytosis Association, the Histiocyte Society, the Erdheim-Chester Disease Global Alliance, and other similar entities are excellent sources of


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education and support for patients, their families, and providers.[6] Providers knowledgeable about AOH can schedule time to educate the patient and family and act as a resource for other providers.[7,8] A proposed list of fundamental educational issues to be discussed with all patients is presented in Table 1.

Neurologic, Musculoskeletal, and Immobility Issues

Neurologic complications of AOH can be devastating and may portend a poor prognosis.[1,9] Patients may develop multiple neurologic abnormalities because different parts of the central and peripheral nervous system can be simultaneously affected. Simultaneous neurologic deficits create treatment challenges for providers and significant care issues for caregivers.[1,2,9] The goal of care is to optimize function and allow the patient to safely remain in their residential environment.[10]

Speech and Swallowing Difficulties

Speech, chewing, and swallowing difficulties may arise from disease in the cerebral cortex, brainstem, cerebellum, or orofacial muscles.[1,9] Expressive speech difficulties can be frustrating for patients and families. Patients may be unable to express important needs and family members may not understand them or may not know how to remedy the communication issue. Speech therapy can help with exercises, communication strategies, and assistive devices. Next, dysphagia can lead to reduced nutritional intake, and can be a safety issue due to the potential for aspiration of food, saliva, or gastroesophageal refluxate, predisposing to respiratory compromise, pneumonia, and sepsis.[11,12] A videofluoroscopic swallow study or endoscopy study can determine which phase (eg, oral, pharyngeal, esophageal) of the swallowing process is affected, and can also identify patients who have difficulty protecting their airway.[11,12] Speech pathologists recommend dietary modifications and teach adaptive maneuvers that minimize aspiration and preserve independence in eating, hopefully reducing the need for gastrostomy tubes. Patients should be screened for warning signs of dysphagia[13] early in the diagnostic process, and with subsequent disease progression. Lastly, the potential efficacy of medications can be reduced if they cannot be safely swallowed or used as recommended. Notably, some medications for histiocytoses are not FDA-approved to be consumed after being crushed, chewed, or liquified.[14–17]

Table 1. Key Educational Issues in AOH

• With some exceptions, AOH are considered incurable chronic illnesses that must be managed
• Disease progression may occur, despite treatment; new manifestations or worsening of previously stable disease may require more testing and new treatments
• Treatment is typically long term, and is usually a combination of pharmacologic, physical, and sometimes invasive therapies (eg, indwelling ureteral stents or surgery)
• Some patients may experience a fatal course of the disorder, despite all available treatment, and it is often difficult to predict prognosis upon diagnosis
• AOH can affect multiple organ systems at different points in the course of the illness, underscoring the importance of regular surveillance and care coordination with various specialists
• Other general health issues should be treated, because the patient's overall health factors into how the disorder can be managed, and into the patient's quality of life

Abbreviation: AOH, adult-onset histiocytoses.

Balance Issues and Fall Risk

AOH can damage various central and peripheral nervous system structures, including motor or sensory cortices, basal ganglia, cerebellum, spinal cord, and peripheral motor and sensory nerves.[1,9,18–20] Additionally, therapy may also cause central or peripheral neurotoxicity.[21] These changes, in combination with ostalgia, fatigue, and asthenia, can create balance, gait, and gross and fine motor coordination difficulties.[22] Deficits can range from mild issues resulting in subtle changes that can be readily addressed with occupational therapy and physical therapy, to profound disability necessitating wheelchairs, personal assistance, home modifications, and even 24-hour care.[1] These changes also increase the risk of falls, which can have serious consequences[23] and are predominant in a patient's permanent residence.[24] Neurologists working with physiatrists and various therapists can assess global functioning, identify deficits, and create a care plan that may include home safety assessments, assistive devices, and rehabilitation.[25]

Self-Care and Dependency Issues

The loss of motor skills, in conjunction with sensory deficits, ataxia, and poor coordination, create challenges in accomplishing essential health behaviors, such as eating, bathing, dressing, and other self-care activities.[26,27] The inability to perform such fundamental daily health behaviors can result in skin breakdown, soft tissue infections (eg, oral infections, skin abscesses), dehydration, protein calorie malnutrition, weight loss, and debility. Some patients require assistance with all care needs, without which they could not survive. Providers can partner with caregivers and patients to assess for functional deficits across various environments, including the home, workplace, and local community. Providers can then enlist the help of various therapists to retrain patients, train caregivers, and find effective resources that make activities of daily living safer. Referrals to community agencies or home care rehabilitation services can be provided to help make home modifications for those at risk (Table 2). Lastly, social workers can help obtain home care and transportation services, allowing

patients to make medical appointments and maintain independence.

Cognitive and Personality Changes

Cognitive difficulty arises from different pathologic processes.[9,28] For patients with AOH, various brain lesions and cerebral atrophy, systemic inflammation, endocrine disorders, mood disorders, and medication side effects (eg, interferon-related pseudoatrophy) can cause cognitive decline.[1,9] Even patients with mild cognitive impairments can experience concentration difficulties or forgetfulness, which may lead to work-related difficulties. More seriously, families may report safety issues such as patients getting lost, leaving on appliances, or financial impulsivity. A careful cognitive evaluation consisting of a detailed history, neurocognitive testing, and perhaps neuropsychologic testing are important steps in the evaluation and treatment of these symptoms.[1] Organic brain pathology can cause psychiatric symptoms,[29] such as pseudobulbar affect in patients with ECD.[9,30] This neurologic complication can be socially disabling and isolating. Notably, education helps patients and their families cope, and dextromethorphan hydrobromide 20 mg/quinidine sulfate 10 mg is an FDA-approved treatment for this condition.[31]

Endocrine Issues

Endocrine dysfunction is a frequent and early occurrence in AOH, which can be disabling and may be lifelong.[32] Manifestations can be due to primary organ disease, or secondary to central dysfunction.[32,33] Moreover, a deficit of ≥3 pituitary hormone axes, termed panhypopituitarism, may occur in some patients with AOH. Early referral to an endocrinologist is warranted.[33,34] Table 3 details the

Table 2. Clinician Resources for Managing Adult-Onset Histiocytoses

Health/Functional Issue	Resources
Provider and patient education about histiocytoses	Histiocytosis Association (https://histio.org/) Histiocyte Society (https://www.histiocytesociety.org/)
Referral sources for the United States and Europe	National Organization for Rare Disorders (https://rarediseases.org/) Memorial Sloan Kettering Cancer Center (https://www.mskcc.org/cancer-care/types/histiocytosis/types-histiocytosis) Texas Children's Hospital (https://www.texaschildrens.org/departments/histiocytosis-program) European Consortium for Histiocytosis (https://www.echo-histio.net/index_eng.html) Histio UK (https://www.histiouk.org/) Erdheim-Chester Disease Global Alliance (https://erdheim-chester.org/)
General disability resources	Americans with Disabilities Act (https://www.ada.gov/ada_fed_resources.htm) USAGov (https://www.usa.gov/disability-services) National Council on Disability (https://ncd.gov/resources) HHS.gov (https://www.hhs.gov/programs/social-services/programs-for-people-with-disabilities/index.html) American Disability Association (https://www.americandisabilityassociation.org/) How To Get On (https://howtogeton.wordpress.com/)
Home modification assistance	Rebuilding Together (https://rebuildingtogether.org/) United Disability Services Foundation (https://udservices.org/) USC Leonard Davis School of Gerontology (https://homemods.org/national-directory/) HomeAdvisor (https://www.homeadvisor.com/r/grants-for-home-modification/)
Resources for the visually impaired Ocular toxicities	American Council of the Blind (https://www.acb.org/) National Federation of the Blind (https://nfb.org/resources) American Foundation for the Blind (https://www.afb.org/blindness-and-low-vision/visionaware) Hadley (https://hadley.edu/) World Blind Union (https://worldblindunion.org/) National Registry of Drug-Induced Ocular Side Effects (http://www.eyedrugregistry.com/)
Provider and patient endocrine resources	American Association of Clinical Endocrinologists (https://pro.aace.com/) Endocrine Society (https://www.endocrine.org/) National Adrenal Diseases Foundation (https://www.nadf.us/) American Thyroid Association (thyroid.org/patients)
Provider and patient neurologic resources	National Institutes of Neurological Disorders and Stroke (https://www.ninds.nih.gov/disorders/support-resources/gov-organizations) The Association for Neurologically Impaired Brain Injured Children (ANIBIC) (http://www.anibic.org/)
Provider and patient kidney disease resources	National Kidney Foundation (https://www.kidney.org/) American Kidney Fund (https://www.kidneyfund.org/loved-one-with-kidney-disease.html) American Association of Kidney Patients (https://aakp.org/) American Nephrology Nurses Association (https://www.annanurse.org/)
Provider and patient skin disease resources	Cancer.net (https://www.cancer.net/) Oncology Nursing Society (https://www.ons.org/articles/ons-guidelinestm-cancer-treatment-related-skin-toxicity)

clinical presentation and management of endocrinopathies in AOH.

Diabetes insipidus is one of the most common endocrinopathies in AOH and if severe, can result in serious fluid and electrolyte disturbances.[1,35–37] Its early detection and treatment with desmopressin may decrease the associated morbidity.[38] Patients and caregivers need education about medication and how to prevent complications such as dehydration.

Hypogonadism can occur in patients of either gender. In men, low levels of testosterone create a variety of symptoms (see Table 3), which can substantially decrease quality of life (QoL). Insufficient testosterone can also cause muscle atrophy and weakness, which can interfere with rehabilitation. Infertility, which is also reported in AOH, is a significant concern for patients planning for families.[1,39,40]

Hypothyroidism is another frequent endocrinopathy in AOH, and its manifestations (see Table 3) can potentially contribute to poor QoL.[41] Thyroid hormone replacement may help improve QoL and ameliorate symptoms. Providers should be aware that dosage adjustments to maintain a euthyroid state may be necessary during the course of the illness.[39–41]

Adrenal gland dysfunction is common in AOH, and is often bilateral.[1,35,42,43] Adrenal insufficiency (AI) has an estimated frequency of 35% in patients with ECD. Central AI is a potentially devastating endocrinopathy in histiocytosis, and regular screening with prompt treatment may reduce morbidity and mortality.[43] Patients and caregivers need education about daily replacement therapy, sick-day rules and stress dosing, and how to identify signs and symptoms of an adrenal crisis, which can be life-threatening (see endocrine resources in Table 2). AI symptoms may overlap with other endocrinopathies and other organ complications, which can create challenges in establishing a diagnosis.

Bone and mineral metabolism abnormalities in AOH can occur due to various osteolytic effects (eg, primary disease effect, uncontrolled endocrinopathies, prolonged immobility, medication side effects). Bone involvement in AOH can affect many structures of the axial and appendicular skeleton, which may limit function due to ostalgia.[1,44] Lastly, bone density loss increases fracture risk, which is especially concerning for patients at risk for falls.

Renal and Urologic Issues

AOH can have various effects on different parts of the urinary system, ranging from mild asymptomatic renal dysfunction to organ failure.[1,30,45–47] Because these adverse effects can be insidious and difficult to localize, a systematic approach ensures that all aspects of the urinary system are investigated.

If kidney disease is identified, treatment is directed toward maintaining renal function and preventing further insults. Nephrologists can help manage comorbid medical conditions, coordinate treatment of complications of kidney disease such as proteinuria, and help providers avoid nephrotoxic drugs. Emergent issues such as severe prerenal and postrenal obstruction in ECD may require invasive medical or surgical intervention.[1,45,48–50] Stenting

Table 3. Endocrine Disorders and Their Management in Patients With Histiocytoses

Endocrine Dysfunction	Clinical Manifestations	Evaluation/Workup	Treatment	Referral
Primary and central hypogonadism	Fatigue, reduced libido, decreased muscle mass, erectile dysfunction, infertility, hot flashes, sparse facial and body hair, osteoporosis/fragility fractures	All patients should have a baseline assessment of serum LH, FSH, 6 a.m. total testosterone × 2 (men), estradiol (women), semen analysis (if infertility is a concern)	Men: replace with oral, intramuscular, transdermal or another parenteral testosterone Childbearing-age women: consider hormone replacement therapy with transdermal or oral estrogen formulations	Endocrinologist or a reproductive specialist
Primary and central adrenal insufficiency	Fatigue, nausea, myalgia, arthralgia, weakness, weight loss, abdominal pain, hypoglycemia	A morning serum cortisol and ACTH followed by ACTH stimulation testing	Supplementation with hydrocortisone at a dose of 10 to 12 mg/body surface area in 1.73 m^2; medical alert bracelet/pocket card; sick day rules and hydrocortisone injection prescription and education	Endocrinologist
Primary and central hypothyroidism	Weight gain, fatigue, myalgia, cold intolerance, headache	Baseline evaluation with a serum TSH, free T4 and T3	Levothyroxine (conventional dose for younger adults is 1.6 mcg/kg body weight) with serial monitoring of free T4 and T3 levels. Goal of therapy to keep free T4 in upper half of normal range	Endocrinologist or a thyroid disease expert

Abbreviations: ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone; TSH, thyroid-stimulating hormone.

of obstructed ureters, the placement of nephrostomy tubes, or use of other urinary drainage systems may preserve renal function. Patients and caregivers require education about the care and risks of these drainage systems. Despite such advanced interventions, some patients progress to end-stage renal disease (ESRD). These patients may require dialysis[1] and some may be candidates for transplantation.[48] ESRD creates significant care management issues and is associated with increased morbidity and mortality, which underscores the need to identify renal disease early and institute timely intervention to preserve renal function (see renal resources in Table 2).

Visual Acuity Loss and Other Ocular Issues

Histiocytic disorders, and their associated therapy, can cause intraocular or extraocular pathology, as well as periorbital pathology, potentially leading to visual loss.[1,2,51–54] Loss of vision can be insidious or may develop rapidly (eg, drug-induced ocular toxicities). This devastating complication may occur at various points in the illness.[2,51] In ECD and RDD, histiocytes accumulating in the retro-orbital space may cause proptosis, resulting in corneal damage from prevention of eyelid closure.[1,55] Unrelieved compression of small-caliber blood vessels, and potentially the optic nerve, may result in ischemic damage.[1,51] Diplopia may also occur from orbital involvement. Additionally, some medications are associated with rare but serious ocular complications, such as retinal vein occlusion[56] and retinopathy, whereas radiation treatment for proptosis may result in cataracts and retinopathy.[57] The National Registry of Drug-Induced Ocular Side Effects is an updated resource to research potential toxicities.[58] See Table 2 for eye resources.

Visual loss increases the risk of sustaining accidents and impairs functioning. Falls, vehicular and machinery accidents, medication errors due to poor vision, and other risks related to visual impairment can result in permanent injury and further functional loss. Additionally, some patients lose driving privileges, creating transportation problems. To minimize such occurrences, low-vison specialists can assess various aspects of visual functioning and recommend modifications and devices that help maintain independence (see Table 2 for vision resources). For patients with significant visual loss, depression and anxiety are complications that can be addressed through various therapies.[59] Lastly, preventing visual loss is a priority survivorship issue, necessitating regular eye examinations, the treatment of comorbid illnesses such as diabetes mellitus and hypertension, and managing the ocular effects of aging, all of which help prevent additional loss.

Cardiovascular and Pulmonary Issues

Cardiac and vascular involvement is described in all AOH and some may be life-threatening.[1,4] Almost all structures of the heart can be involved.[60,61] In ECD, myocardial or pericardial histiocytic infiltration and inflammation can cause tamponade resulting in heart failure[62] and may require urgent intervention to maintain cardiac output.[62,63] Histiocytic infiltration of electrical conducting tissue can cause significant arrhythmias and conduction defects, necessitating pharmacotherapy or pacemaker placement.[1] In ECD, coating of the smaller branches of the aorta may cause stenosis and possibly ischemia. Thus, cardiology consultation is essential for the evaluation and treatment of the various cardiac and vascular manifestations, including drug-induced cardiovascular toxicity. Baseline cardiac studies can be compared with subsequent studies to identify early and important changes. Lastly, some patients with AOH have an increased frequency of metabolic abnormalities, and these conditions may exacerbate other comorbid medical problems, thereby increasing the risk for cardiovascular disease, which warrants screening and counseling.[39]

AOH can cause various forms of lung disease.[1,44,64,65] Histiocytic infiltration of lung tissues can result in intrathoracic lymphadenopathy, pleural effusions, airway disease, or an interstitial lung disease.[66] Pulmonary involvement can cause debilitating dyspnea, fatigue, and cough.[1,44,65] These symptoms may be attributed to other problems (eg, cardiac disease), leading to the possibility of lung disease being missed until significant compromise of pulmonary function occurs. Progressive lung disease, sometimes seen in AOH, may require supplemental oxygen and substantial lifestyle modifications, and may be fatal.[1,4,44] Pulmonologists can assess respiratory function and initiate pulmonary rehabilitation. Therapists teach energy conservation principles to reduce the work of breathing; techniques for fatigue management; exercises to strengthen accessory respiratory muscles; and adaptive lifestyle changes.

Dermatologic Issues

The histiocytoses produce a variety of skin lesions that can be difficult to manage and may create social embarrassment.[1,4,67,68] Patients with ECD may have lesions appearing on many skin surfaces, but characteristically manifest as periorbital xanthelasmas. Medications such as BRAF and MEK inhibitors are associated with an increased risk of skin cancers, as well as other skin lesions, which can occur at various points during therapy.[69–71] Palmar-plantar erythrodysesthesia (hand-foot syndrome) tends to occur during the first few months of therapy, which can be severe if untreated and may result in interruption of therapy. Other agents used as treatments for histiocytoses also have dermatotoxicity, and dermatologists can help manage common adverse events affecting the skin.[72] Treatment guidelines are available at ASCO.org.

Psychological and Psychosocial Issues

Despite treatment, some patients are unable to return to premorbid levels of functioning, which can have life-changing consequences for patients and their families.

This is especially relevant for disabled long-term survivors, whose care needs may tax family resources. These changes may lead some patients to develop mood disorders and loss of self-esteem or self-worth issues as they confront permanent physical and cognitive limitations. Moreover, job loss may result in lost income and may threaten healthcare access due to loss of medical insurance and other resources, thereby magnifying the stress of adapting to permanent physical changes. This is particularly relevant for AOH disorders, which often require high-cost care from multiple specialists. Meanwhile, the requirements of everyday life continue despite the patient's illness, leaving others to assume multiple roles, including increasing their work responsibilities to mitigate family income loss to secure medical care and other necessities.

Social interactions, interpersonal bonds, and leisure activities are important stimuli for patients. These connections and activities are fundamental to QoL, especially for those who are physically dependent. Unfortunately, some patients have difficulty maintaining relationships with their spouse, other family members, friends, and colleagues. Such patients may lose meaningful social contacts, leading to depression and hopelessness. These "invisible wounds" can aggravate physical issues such as chronic pain[73] and may be associated with poor outcomes, especially in older, chronically ill adults.[74] Referrals to counselors and patient support and advocacy groups can be therapeutic and may generate valuable insights that improve social interactions.

Conclusions

AOH are rare and potentially serious disorders that frequently pose difficult diagnostic and management challenges for providers. The multiple and often overlapping manifestations create numerous survivorship issues for patients and caregivers. For some, these disorders can be debilitating, resulting in loss of income, independence, and the ability to perform necessary self-care and other important daily activities. Prognosis varies according to many factors, and care needs for long-term survivors with AOH may strain family support and other resources. These profound alterations in patients' lives underscore the importance of considering their illness in the context of their life and their available resources. Awareness of these important issues can help providers marshal effective resources to optimize patient health and QoL.

Submitted July 6, 2021; accepted for publication September 22, 2021.

Author contributions: *Patient care:* O'Brien, Dave, Shekhar, Hannah-Shmouni, Comis, Solomon, Chen, FitzGibbon, Gochuico, Estrada-Veras. *Data creation, entry, and analysis:* O'Brien, Dave, Shekhar, Hannah-Shmouni, Comis, Solomon, Chen, Gochuico, Estrada-Veras. *Manuscript preparation:* All authors.

Disclosures: Dr. Dave has disclosed receiving grant/research support and consulting fees from and serving as a scientific advisor for Novartis Pharmaceuticals.

Funding: This work was supported in part by the Intramural Research Programs of the National Human Genome Research Institute; the National Heart, Lung, and Blood Institute; the Rehabilitation Medicine Department at the NIH Clinical Center; the Speech Language Pathology Section of the Rehabilitation Medicine Department at the NIH Clinical Center; Eunice Kennedy Shriver National Institute of Child Health and Human Development; the National Eye Institute, NIH; Clinical Research Branch, National Institute of Environmental Health Sciences, NIH; the National Institute of Neurologic Disorders and Stroke; and the Warren Grant Magnuson Clinical Center, NIH.

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Survivorship Issues in Adult Patients With Histiocytic Neoplasms

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J Natl Compr Canc Netw 2021;19(11):1312–1318

eAppendix 1: Oral and Otolaryngological Issues

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Almost all oral and otolaryngological structures can be affected by adult-onset histiocytoses (AOH).[1–5] Mandibular and maxillary involvement, periodontal disease, all can erode bone, causing pain and tooth loss,[1,3] which may interfere with chewing, predisposing to dysphagia.[5] Chronic xerostomia increases the risk of caries, buccal and tongue ulcers, infections (especially candidiasis), tooth and gum loss, dysarthria and dysphagia, and halitosis.[6] Some medications and treatments can exacerbate xerostomia (eg, anticholinergics, antihistamines, chemotherapeutics, therapeutic radiation), and the regular use of moisturizing agents may help.[6] Frequent oral care (every 3 to 6 months) with careful surveillance of tooth and bone integrity (especially alveolar bone), salivary structures, and inspection for aphthae and signs of infection is warranted.

The 4 sinus cavities and their surrounding bony structures, the facial bones and mandible, and the calvarium and skull base can all be sites of histiocytic disease activity.[4,5,7–9] Untreated proliferative disease with attendant inflammation can cause erosion into the orbit, ear canal, or middle ear compartment, endangering visual or otologic structures.[10,11] Patients with infiltrative disease activity into, or originating from, these bony compartments may present with nondescript or common symptoms, such as ear/eye pain, signs of otitis externa/media, otorrhea, sinusitis, periorbital or periauricular swelling, or visual changes.[7,9,11–13] The underlying etiology for these symptoms may not be immediately obvious given that histiocytic (ie, neoplastic) disease activity deep in the skull and facial bones may not be readily apparent on an external examination using only routine office equipment[9,12,14]; therefore, the appearance of such symptoms in a patient with known or suspected histiocytosis should prompt consultation with an evaluation for both common causes, and for histiocytic disease activity to prevent serious complications (ie, permanent visual and hearing/vestibular function loss).[4,9] The possibility of such complications underscores the importance of regular surveillance examsinations by care team members.

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