Case report

Multisystem Langerhans Cell Histiocytosis in an infant ☆

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A B S T R A C T

Langerhans cell histiocytosis (LCH) is a rare enigmatic disease that pre-dominantly affects children under 5 years of age. We report an interesting case of a 5 month old female diagnosed with multisystem LCH. Her disease process included osseous, pulmonary, gastrointestinal, cutaneous, hematopoietic and neurologic involvement. This case highlights the varying clinical symptoms, risk factors, pathogenesis, and management of multisystem LCH. This case also emphasizes the role of diagnostic imaging in this multifaceted disease.

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Introduction

Langerhans cell histiocytosis (LCH) is a rare disease resulting from clonal proliferation of abnormal macrophages. These cells arise from the bone marrow and induce bone resorption, creating their characteristic lytic bone lesions. The risk factors are not well understood; it is hypothesized to be a reactive disorder [1]. Incidence rates have been reported as 5 cases per million per year overall with most cases presenting before the age of 5 [2–3]. LCH occurs in adults as well, typically manifesting as pulmonary LCH and is associated with smoking [4]. In children the disease commonly presents via osseous lesions, however dissemination into other organ systems can result, as this case demonstrates. Differential diagnostic considerations for multisystem LCH depend on which organs are affected and thus can be very broad. The variable presentation of LCH makes diagnosis challenging and ultimately tissue sampling is needed for definitive diagnosis.

Case presentation

Here we present a 5-month-old female with failure to thrive, anemia and elevated inflammatory markers of unknown etiology. The patient was born at term with an uncompli-

Fig. 1 – Chest Radiograph at 2 months of age demonstrates perihilar fullness with peribronchial wall thickening and linear reticulonodular opacities. No osseous lesions are identified.
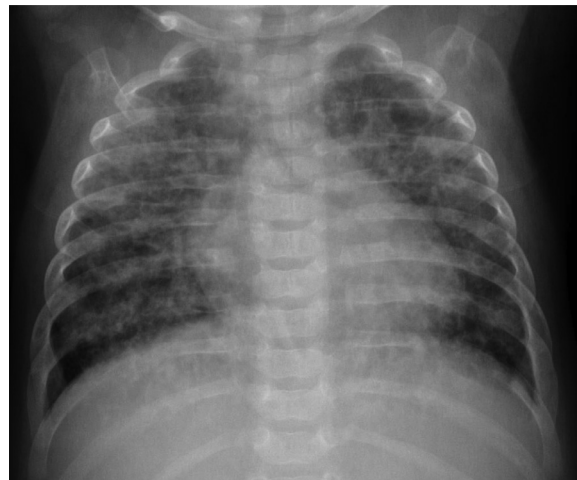

Fig. 2 – Chest Radiograph at 5 months of age demonstrates increased diffuse interstitial markings and granular opacities throughout the bilateral lungs with peribronchial cuffing.

cated prenatal and early postnatal course. At approximately 2 months of age she experienced a drop in weight to the 2nd percentile, from her birthweight in the 20th percentile. She concurrently developed intermittent tachypnea, yellow and brown cutaneous papules, and greasy stools which demonstrated occasional specks of blood. Chest radiograph at the time showed linear reticular opacities with a nodular component (Fig. 1). The infant's growth was closely followed over the next 2 months, however her weight continued to drop to below the 1st percentile, her length also down-trended to less than the 1st percentile and her head circumference had dropped to the 10th percentile. These changes all occurred despite lifestyle modifications including maternal avoidance of dairy and soy, as well as a trial of hydrolyzed formula due to presumed diagnosis of a milk protein allergy. The patient was subsequently admitted for inpatient observation and evaluation at 4 months of age for failure to thrive and closer monitoring of her caloric intake. Further workup for additional causes of failure to thrive was initiated. Laboratory analysis continued to demonstrate anemia and elevated inflammatory markers. Milk protein allergy remained the presumed diagnosis, so she was treated with iron supplementation. The patient was able to gain appropriate weight after implementation of a strict feeding plan during her admission, and subsequently her poor growth was attributed to inadequate caloric intake. With the improvement in growth, the patient was discharged. Over the next month, during subsequent clinic visits, the patient's growth plateaued despite following the appropriate feeding plan. She additionally continued to have worsening anemia, up-trending inflammatory markers, and thrombocytosis. Chest radiograph performed at this time demonstrated worsening interstitial and granular opacities (Fig. 2). With her declining clinical condition, worsening imaging findings and abnormal laboratory analysis she was admitted to a tertiary medical center for further evaluation.

Aside from mild tachypnea without hypoxia, the initial evaluation at the tertiary care center was notable for a tender soft tissue prominence over her right temporal area, diffuse yellow and brown skin papules and perceived tenderness to palpation over several bony locations including her skull, bilateral axilla and bilateral lower extremities. Due to the soft tissue prominence of the temporal region, a skull radiograph was obtained that showed scattered lytic lesions (Fig. 3). Given concern for the lytic lesions, further diagnostic imaging was performed to include a skeletal survey, abdominal ultrasound, chest CT, and MRI of the brain and spine. The patient was found to have innumerable lytic lesions throughout the axial and appendicular skeleton on the skeletal survey (Fig. 4–6) and diffuse pulmonary nodules and cysts were seen on the chest CT (Fig. 7). At this time, there was no evidence of liver, spleen, kidney, brain or spinal cord involvement on the ultrasound or MRI. Notable laboratory analysis included persistent anemia with a hematocrit of 21%, thrombocytosis to $763 \times 10^3/\mu L$, elevated CRP at 9.5 mg/dL, and elevated ESR of 103 mm/hr. The initial white blood cell count, absolute neutrophil count, ferritin, iron studies, electrolytes, renal function, hepatic function, and thyroid studies were within normal limits. A bone marrow biopsy was obtained which demonstrated occasional clusters of Langerhans cells with positive CD1a staining. This constellation of findings supported the diagnosis of multisystem Langerhans cell histiocytosis (LCH). Given the pathologic diagnosis and her history of intermittent bloody diarrhea, an esophagogastroduodenoscopy (EGD) and flexible sigmoidoscopy were performed with biopsies demonstrating colonic mucosal involvement by LCH.

The patient was subsequently enrolled in the LCH-IV International Collaborative Treatment Protocol for Children and Adolescents with LCH which included weekly dosing of vinblastine and therapy with prednisone. The first seven weeks of therapy were well tolerated. Repeat imaging at this time
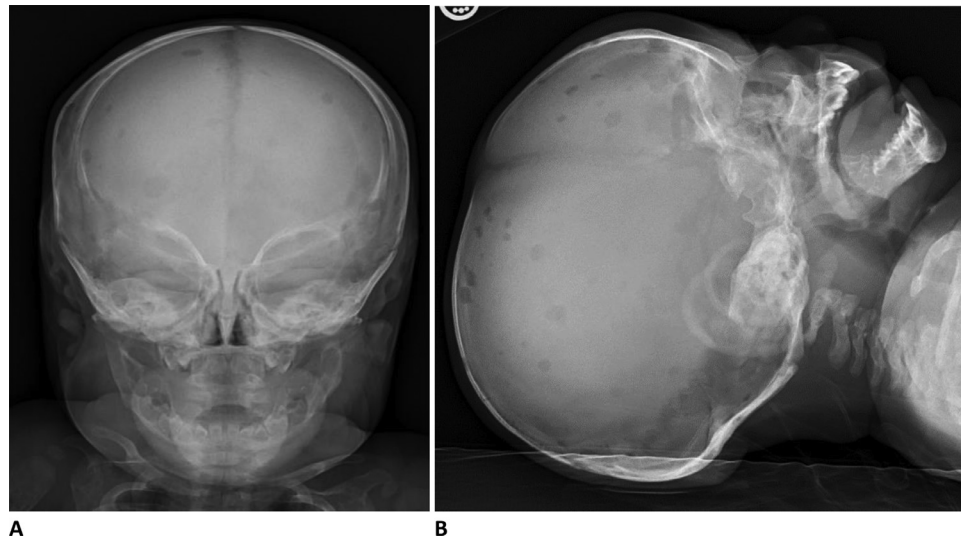
Fig. 3 – Scattered lytic lesions seen throughout the calvarium on frontal (A) and lateral (B) projections which demonstrate narrow zones of transition. This finding is highly suggestive of Langerhans cell histiocytosis.
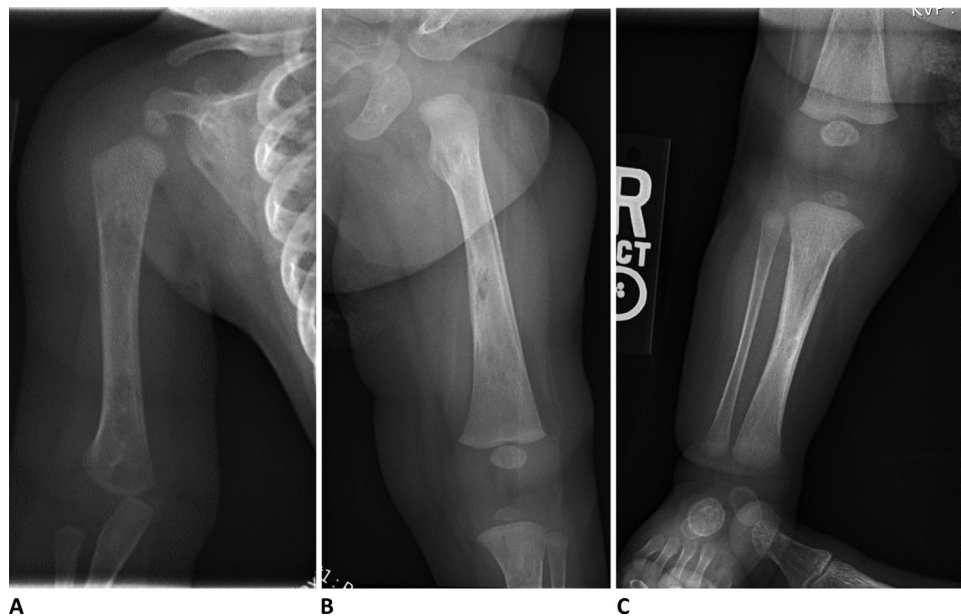

Fig. 4 – Aside from lesions seen in the skull, additional innumerable lytic lesions found throughout appendicular skeleton. Representative lesions in the right humerus (A), left femur (B) and right tibia (C).

revealed improved, though persistent pulmonary involvement (Fig. 8) and decreased size of the osseous lesions (Fig. 9). On clinical exam there was resolution of the skin lesions and improved weight gain. Despite these improvements, however, MRI brain at this time showed loss of the normal signal seen within the neurohypophysis. This finding correlated with the patient's new clinical symptoms of diabetes insipidus and suggested new central nervous system (CNS) involvement (Fig. 10). Diagnostic evaluation after 13 weeks of treatment demonstrated persistent loss of signal in the neurohypophysis, resolution of osseous lesions in the skull (Fig. 11), and unchanged pulmonary involvement (Fig. 12). At this time, the infant is continuing with therapy and follow-up imaging as part of the treatment protocol.

Discussion

Langerhans cell histiocytosis (LCH) is a rare disease resulting from clonal proliferation of abnormal macrophages. These abnormal cells arise from the bone marrow and induce bone resorption, creating the characteristic lytic bone lesions seen
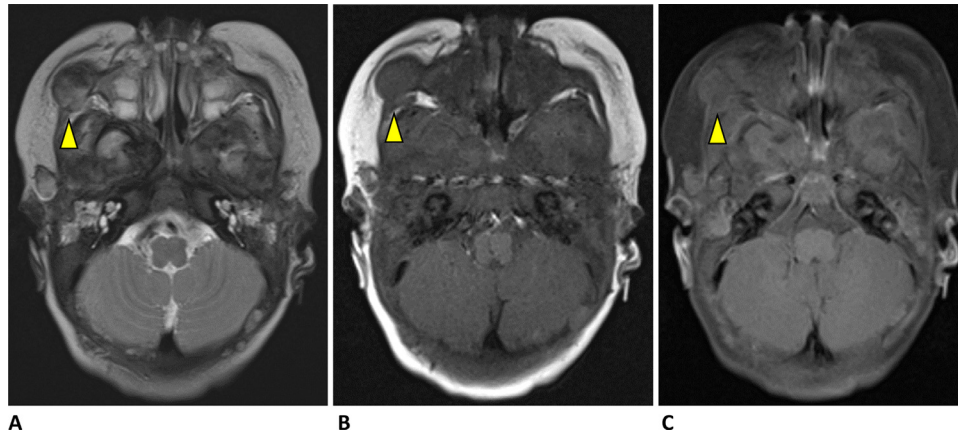
Fig. 5 – Axial T2 (A), T1 (B), and T1 fat-suppressed post contrast imaging (C) demonstrate a 1.8 cm T1 isointense lesion (yellow arrowheads) within the right zygomatic bone which is T2 heterogeneously intense and demonstrates mild enhancement.
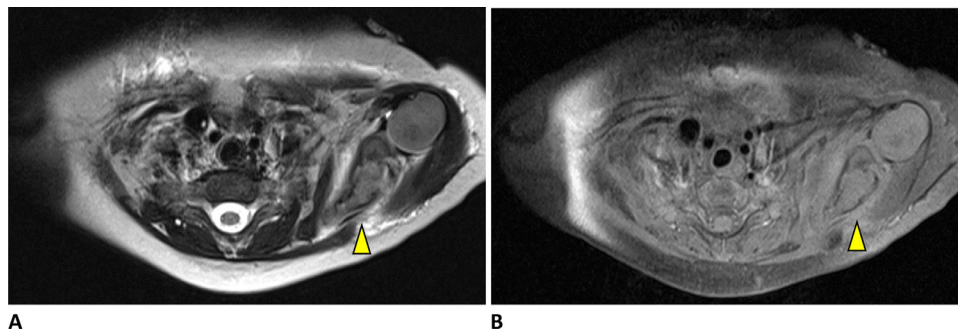

Fig. 6 – T2 hyperintense lesions in the left scapula (yellow arrowheads) (A) which enhances on T1 fat-saturated post contrast imaging (B).
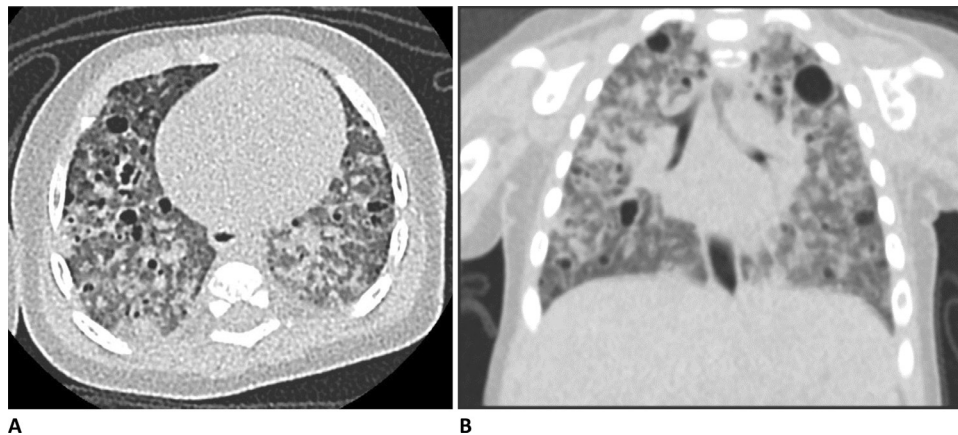

Fig. 7 – Axial (A) and Coronal (B) CT chest without contrast show diffuse pulmonary cysts and nodules with intervening ground glass opacities.

on imaging. It is not completely clear what causes the events leading to abnormal cell proliferation. Some studies have found associations between development of LCH and neonatal infections, as well as under-vaccination, which supports one hypothesis that LCH is a reactive disorder [1]. While the disease commonly presents with skeletal involvement, dissemination to other organ systems can result in a variety of extra-osseous manifestations as were presented in this case. Extra-osseous LCH is rare with incidence rates having been reported as 5 cases per million per year, with most
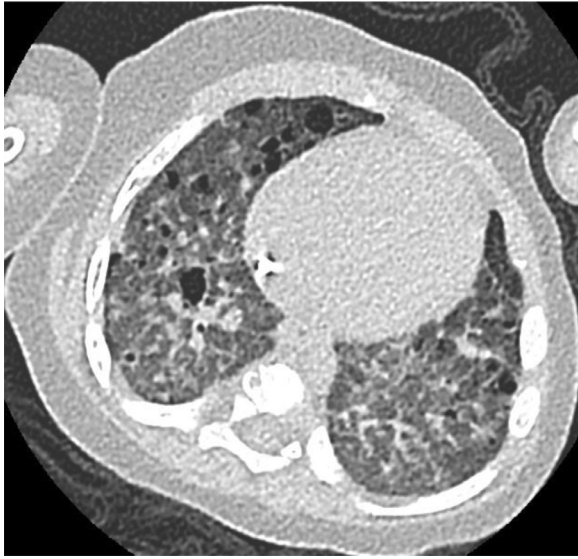
Fig. 8 – Axial CT chest without contrast at week seven of treatment demonstrates persistent diffuse pulmonary cysts and intervening ground glass opacities with reduction in number and size of the pulmonary nodules.

cases presenting before the age of 5 [2−3]. LCH also occurs in adults, typically as pulmonary LCH and has an association with smoking [4]. LCH is often an incidental finding when diagnosed as patients are typically asymptomatic being evaluated for other entities, especially with single system disease.

LCH can be broadly classified into two disease groups: single system and multi-system disease. Presentation of multi-system LCH depends on the organs affected, which may include the soft tissues, skin, central nervous system, lungs, lymph nodes, bone marrow, hepatobiliary system, spleen, salivary glands and GI tract [5]. Multi-system LCH patients are at higher risk for complications due to systemic inflammatory processes which will manifest as weight loss or fever. Cytopenia is another complication of the disease, particularly with

involvement of high-risk organs such as bone marrow, liver, or spleen. Central nervous system (CNS) involvement can result in diabetes insipidus, obstructive hydrocephalus, or neurodegeneration. While single system disease is the most common manifestation in the overall pediatric population, one study suggests that among neonates and infants, multi-system LCH is the predominant presentation [6].

Treatment for LCH again varies depending on the specific organs affected and can include combinations of steroids, chemotherapy, radiation and surgical excision. Solitary osseous lesions can be treated with curettage alone. Per the LCH-III protocol, multisystem LCH is initially treated with 6 weeks of vinblastine and prednisolone [7−8]. If there is evidence of treatment response, then this therapy may be extended for up to 12 months. Poor response or involvement of high-risk organs may necessitate addition of second line agents. CNS involvement in particular would require agents capable of crossing the blood brain barrier such as cladribine, clorfarabine or cytarabine. Those with diabetes insipidus will require vasopressin replacement therapy, which will continue after completion of the chemotherapy regimen [9−10].

Diagnosis by imaging alone is challenging and often not possible. The differential diagnosis for any organ involved is broad and includes a variety of infectious, neoplastic or autoimmune process. With the non-specific imaging appearance of LCH and its variable clinical presentation, the diagnosis of LCH ultimately relies on tissue sampling. The primary roles of diagnostic imaging are to screen for LCH if suspected, to evaluate extent of disease, to confirm multi-system involvement and to monitor treatment response [11].

Once LCH is suspected, the initial imaging workup should start with a skeletal survey. Since osseous lesions are the most common manifestation of LCH, presenting in approximately 80% of cases, skeletal radiographs are the best screening tool as they are widely available, provide minimal radiation exposure and have the greatest chance of detecting abnormalities. Radiographically, osseous lesions in LCH typically present in the skull and long bones as solitary or multiple lytic lesions which lack a sclerotic margin. Cross-sectional imaging with CT or MRI can play a role in better characterizing extent within
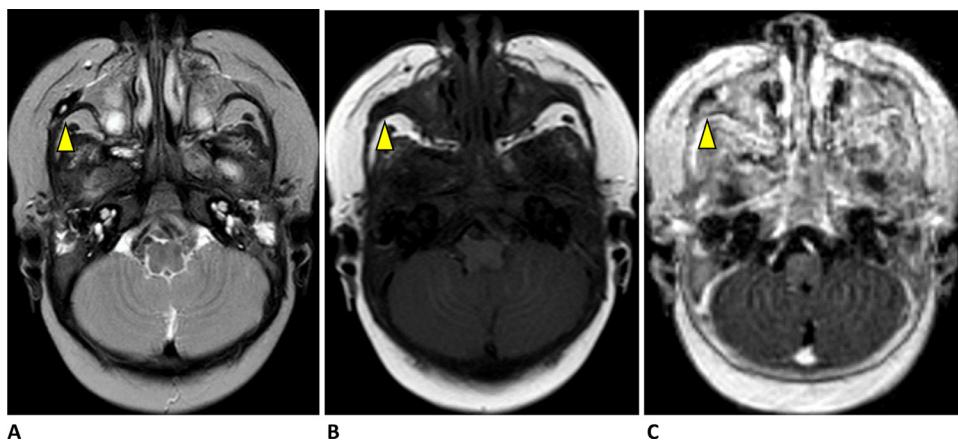

Fig. 9 – Axial T2 (A), T1 (B), and T1 post contrast (C) imaging demonstrate a reduction of T1 isointense lesion (yellow arrowheads) within the right zygomatic bone.
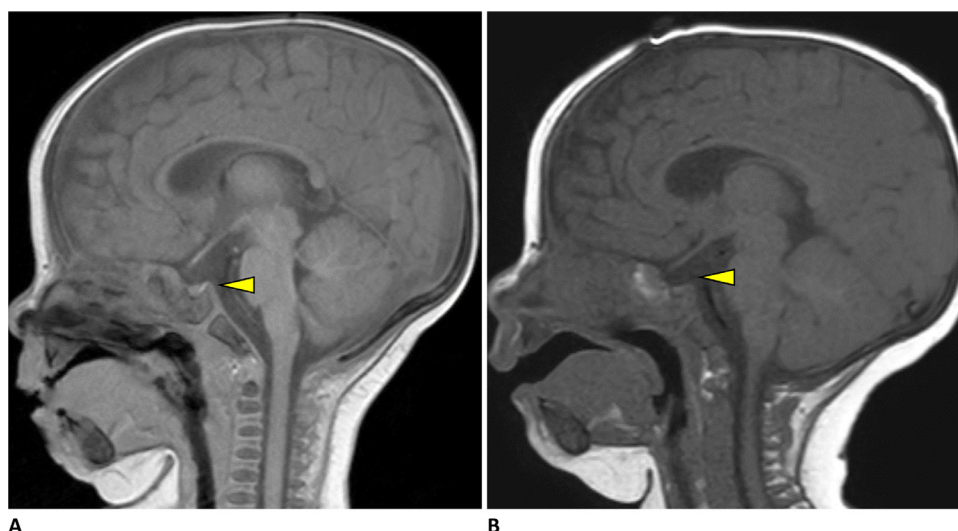
Fig. 10 – Sagittal T1 (A) at initial diagnosis demonstrating posterior pituitary with normal hyperintense signal; sagittal T1 (B) at treatment week seven demonstrate loss of the normal signal (yellow arrows).
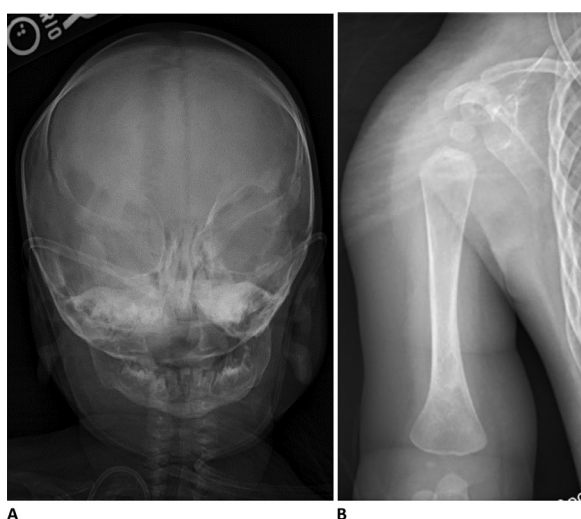

Fig. 11 – Radiographs of the skull (A) and right humerus (B) at week 13 of treatment demonstrate resolution of the previously seen lytic lesions.

the medullary cavity, cortical destruction, and presence of associated soft tissue masses [12]. When assessing for treatment response, findings suggestive of remission include increased density within the lesion, marginal sclerosis, thickening of the cortical bone and normal appearing medullary cavity. Lesions of the skull or spine revealed on skeletal survey should be followed with dedicated MRI, due to an increased risk of CNS involvement.

Central nervous system involvement should be suspected if there are neurologic or endocrine abnormalities. CNS involvement should be evaluated with MRI of the brain. Specific attention should be paid to the hypothalamic-pituitary axis as loss of the normal posterior pituitary T1 hyperintensity in commonly seen in patients with diabetes insipidus [13]. There may also be enlargement of the pituitary stalk, enlargement of the hypothalamus or presence of enhancement. However,

resolution of these findings does not necessarily infer resolution of diabetes insipidus, which can still persist. Lesions can also be found anywhere along the brain or spine, though common areas involved include the cerebellum, basal ganglia and brainstem.

If the chest radiograph or clinical symptoms are suggestive of pulmonary involvement, this can be further evaluated with low-dose CT of the chest. Pulmonary LCH is characterized by upper lobe predominant reticulonodular opacities, cysts and emphysematous changes. These findings may mimic other pulmonary disease processes including emphysema, sarcoidosis, and interstitial pneumonia. Chest CT is the preferred imaging modality for follow up imaging, as pulmonary findings can be subtle and even symptomatic patients may have normal appearing chest radiographs. CT also plays a role in selecting a target site for lung biopsy if needed.

Gastrointestinal findings are perhaps the least specific out of all organs. When the gastrointestinal tract is involved, imaging can demonstrate a hazy mesentery and circumferential bowel wall thickening with possible focal narrowing or dilation. To the best of our knowledge, no imaging study is specifically indicated when gastrointestinal involvement is suspected. Rather, direct visualization and tissue sampling with endoscopy remains the gold standard. Although not classified as a high-risk organ, gastrointestinal involvement carries a poor prognosis, though the mechanism is unclear. Symptomatic involvement may simply have a higher association with extensive spread of systemic disease or potentially negatively affect nutrition [14]. Therefore, despite the low specificity of imaging, recognition of bowel involvement may prompt further investigation and aid in prognostication.

As with other parts of the body, hepatic involvement typically presents as discrete nodules in addition to nonspecific hepatomegaly, steatosis, inflammation and fibrosis. Further imaging with either ultrasound, MRI of the liver or MRCP may be indicated in the setting of abnormal liver function. However, as the disease progresses, involvement can be more diffuse and extensive, eventually leading to sclerosing cholangi-
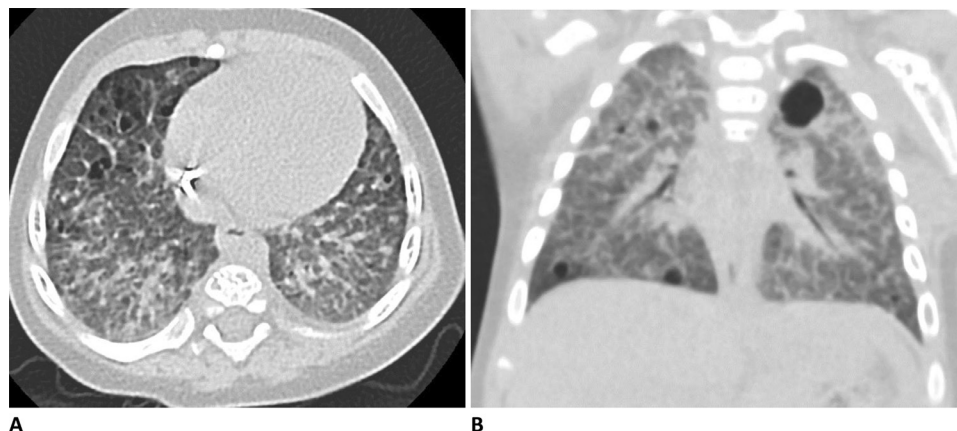
Fig. 12 – Axial (A) and Coronal (B) CT of the chest at week 13 of treatment demonstrates persistent diffuse ground glass opacity throughout the lung parenchyma with innumerable reticular nodular opacities and thin-walled cysts.

tis and cirrhosis. Even in cases of treated LCH, the initial insult to the liver may be so severe that the cycle of inflammatory damage continues, resulting in disease advancement without active lesions. The association with liver failure makes hepatic involvement the most lethal of the high-risk organs, carrying a 51.8% 3-year survival rate compared to 96.7% in those without hepatic involvement [15]. For comparison, the 5-year survival rate for high-risk organ involvement overall is 77.0% compared to a survival rate of 95.4% in LCH overall and 98.4% in multi-system LCH without high-risk organ involvement [16]. The role of imaging is therefore critical in both early confirmation of hepatic involvement and determining disease progression.

Conclusion

Langerhans cell histiocytosis is a rare disease that can have significant morbidity and mortality, especially when it involves more than just the osseous structures. Its variable organ involvement and nonspecific clinical presentation can make early recognition difficult and potentially delay treatment. This case highlights these key points and underscores the crucial role of imaging, which can assist in a prompt diagnosis and aid in determining the extent of disease.

Patient consent

All images used are non-identifiable and all personal information has been removed from the provided diagnostic images. No formal patient consent is required.

Disclaimer

The views expressed in this article are those of the authors and do not reflect the official policy of the Department of the Army, the Department of Defense, or the U.S. Government.

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