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Langerhans Cell Histiocytosis and Erdheim-Chester Disease: A Case Report of Atypical Imaging Overlap

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Abstract: Histiocytoses are rare disorders characterized by abnormal proliferation of histiocytic cells in tissues and organs. They have a broad clinical spectrum and are traditionally categorized as Langerhans cell histiocytosis (LCH) and non-Langerhans cell histiocytosis (N-LCH), but recent evidence highlights a molecular and clinical overlap between LCH and a type of N-LCH known as Erdheim-Chester disease (ECD). While both disorders have distinct features, up to 20% of ECD patients may present with concurrent LCH lesions. Overlap between LCH and ECD is increasingly recognized, but reports of imaging of this phenomenon are scarce. Here, we present a rare case of directly contiguous LCH and ECD lesions in a 69-year-old woman and discuss the radiologic and histopathologic findings as well as the classification of these findings within the revised histiocytosis system.

Keywords: *Langerhans cell histiocytosis, Erdheim-Chester disease, musculoskeletal radiology, lytic bone lesion, sclerotic bone lesion*

Introduction

Langerhans cell histiocytosis (LCH) and Erdheim-Chester disease (ECD) are rare histiocytoses, each with distinct radiologic, histologic, and clinical features. While overlap between LCH and ECD is an increasingly recognized phenomenon—up to 20% of patients with ECD may be found to have concurrent LCH lesions elsewhere in their body[1]—it is rarely discussed in radiologic literature. We report the case of a 69-year-old woman with directly contiguous LCH and ECD lesions. This case report was prepared following the CARE guidelines.[2]

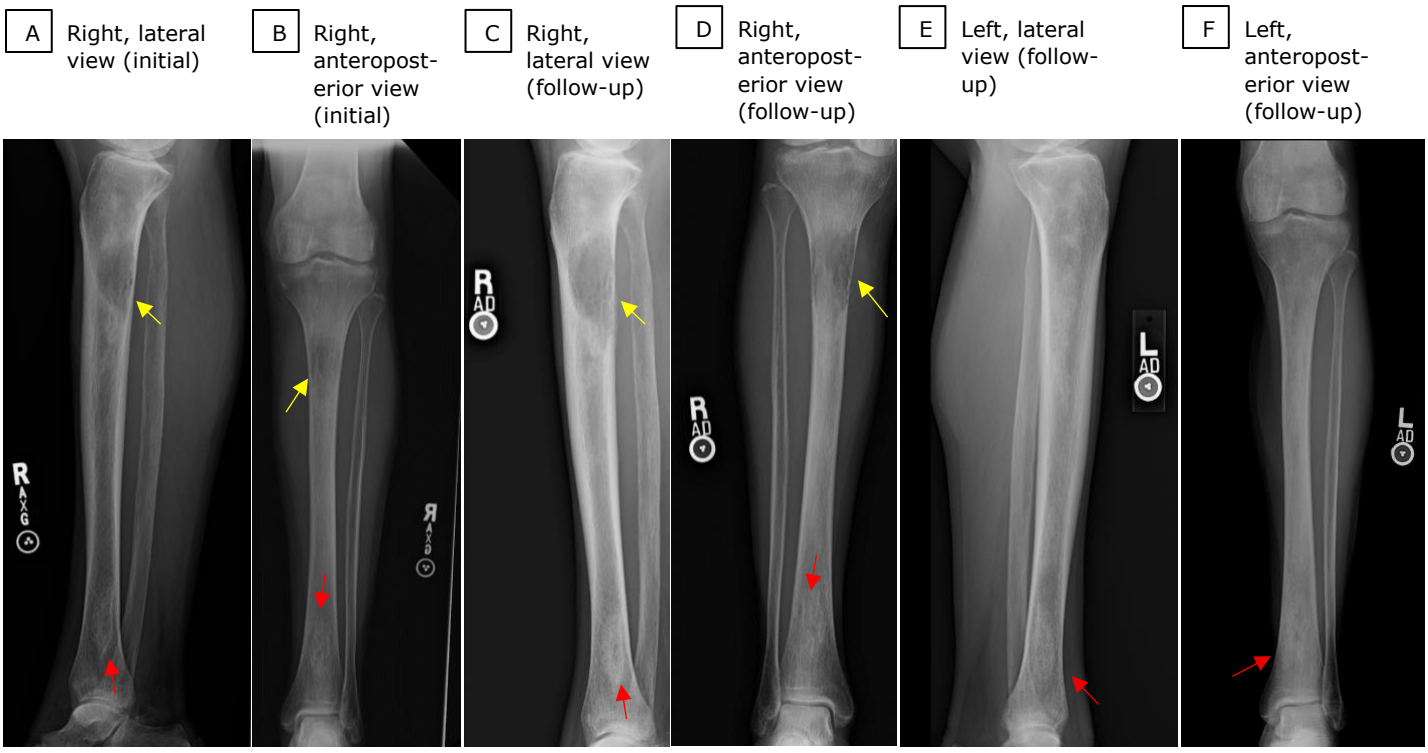
Key Points

- Langerhans cell histiocytosis (LCH) and Erdheim-Chester disease (ECD) are rare histiocytoses with broad clinical spectra.
- Mixed LCH and ECD is an increasingly recognized phenomenon, and recent evidence highlights a molecular and clinical overlap between the two entities.
- On imaging, ECD is characterized by symmetric bilateral intramedullary osteosclerosis in the metadiaphyseal region of the long bones, while LCH presents as permeative, aggressive lytic lesions with other destructive characteristics.
- Awareness of concurrent LCH and ECD lesions can help guide imaging and pathologic diagnosis.

Case Presentation

A 69-year-old woman with a history of hyperlipidemia, hypertension, paroxysmal atrial fibrillation, and chronic ischemic right middle cerebral artery stroke presented to the emergency

Figure 1. Radiography of the Right and the Left Tibia and Fibula in a 69-Year-Old Woman with Mixed Langerhans Cell Histiocytosis Erdheim-Chester Disease.

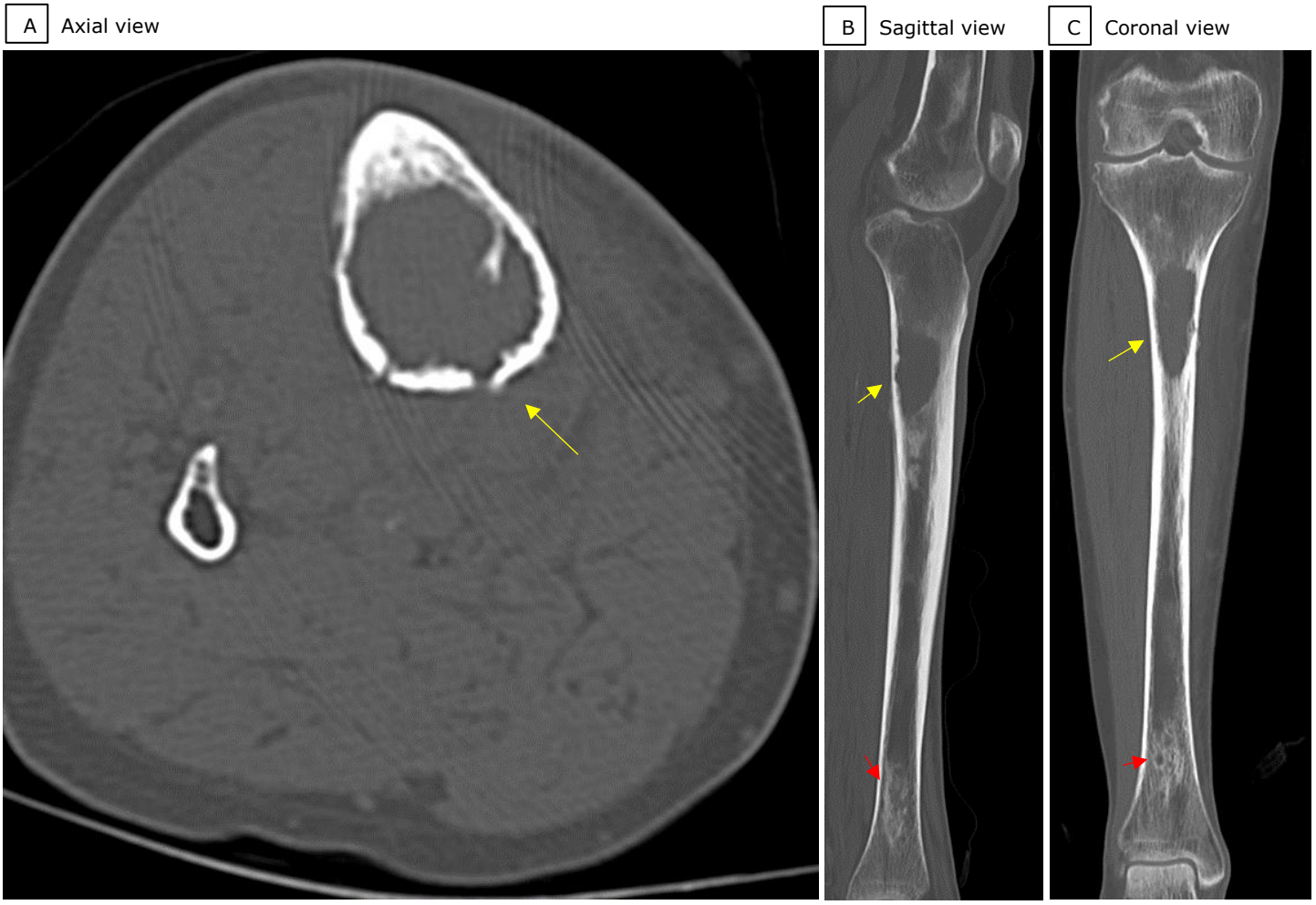


(A, B) Initial lateral and anteroposterior radiographs of the right tibia and fibula demonstrate a 4.5-cm-long lytic lesion with mild posterior endosteal scalloping in the proximal tibial diaphysis (A, B yellow arrows). No pathologic fracture is seen. There is heterogeneous sclerosis in the distal tibial shaft (A, B red arrows).
(C, D) Radiographs of the right tibia and fibula obtained at the time of the patient's second presentation to the ED and subsequent admission demonstrate a 4.5-cm lytic lesion in the proximal tibial diaphysis (C, D yellow arrows) with mild posterior endosteal scalloping. Note, this lesion measured 7.4 cm on MRI images taken during the same period (Figure 3A).There is no visible pathologic fracture. There are scattered intramedullary sclerotic densities in the distal femur and the proximal and distal tibia (C, D red arrows).
(E, F) Radiographs of the left tibia and fibula demonstrate scattered intramedullary sclerotic densities (red arrows) in the distal femur and throughout the tibia. These densities appear symmetric with those identified in the patient's right leg (C, D).

department with pain in the right tibia that persisted after minor direct trauma 10 days prior. Initial radiographs (Figure 1A and 1B) and computed tomography (CT) images (Figure 2) revealed a destructive lytic lesion in the proximal right tibia with cortical breakthrough and a soft tissue mass. This mass measured 4.5 cm on radiographs and 5 cm on CT images. There was also scattered intramedullary sclerosis in the mid and distal right tibia. The patient was discharged with an appointment scheduled for outpatient follow-up with orthopedic oncology.

One month later, before the scheduled follow-up could take place, the patient returned to the emergency department after two falls at home and was experiencing worsening pain in the right tibia. This prompted her admission for expedited workup. Radiographs showed rapid progression of the lytic lesion in the proximal right tibia without pathologic fracture (Figure 1C and 1D). Contralateral tibia radiographs revealed symmetric intramedullary sclerosis in the left tibia (Figure 1E and 1F). Subsequent magnetic resonance imaging (MRI) of the right tibia provided further evidence of the destructive growth of the lytic lesion in the proximal tibia, which was measured at 7.4 cm (Figure 3). MRI also showed contiguous enhancing sclerotic lesions extending toward the distal tibia (Figure 3B and 3C). CT imaging of the chest, abdomen, and pelvis showed no additional lesions or metastatic disease. Laboratory results revealed slightly elevated C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), but the results of a serum protein electrophoresis (SPEP) test showed no aberrations.

Figure 2. Computed Tomography of the Right Tibia in a 69-Year-Old Woman with Mixed Langerhans Cell Histiocytosis Erdheim-Chester Disease.



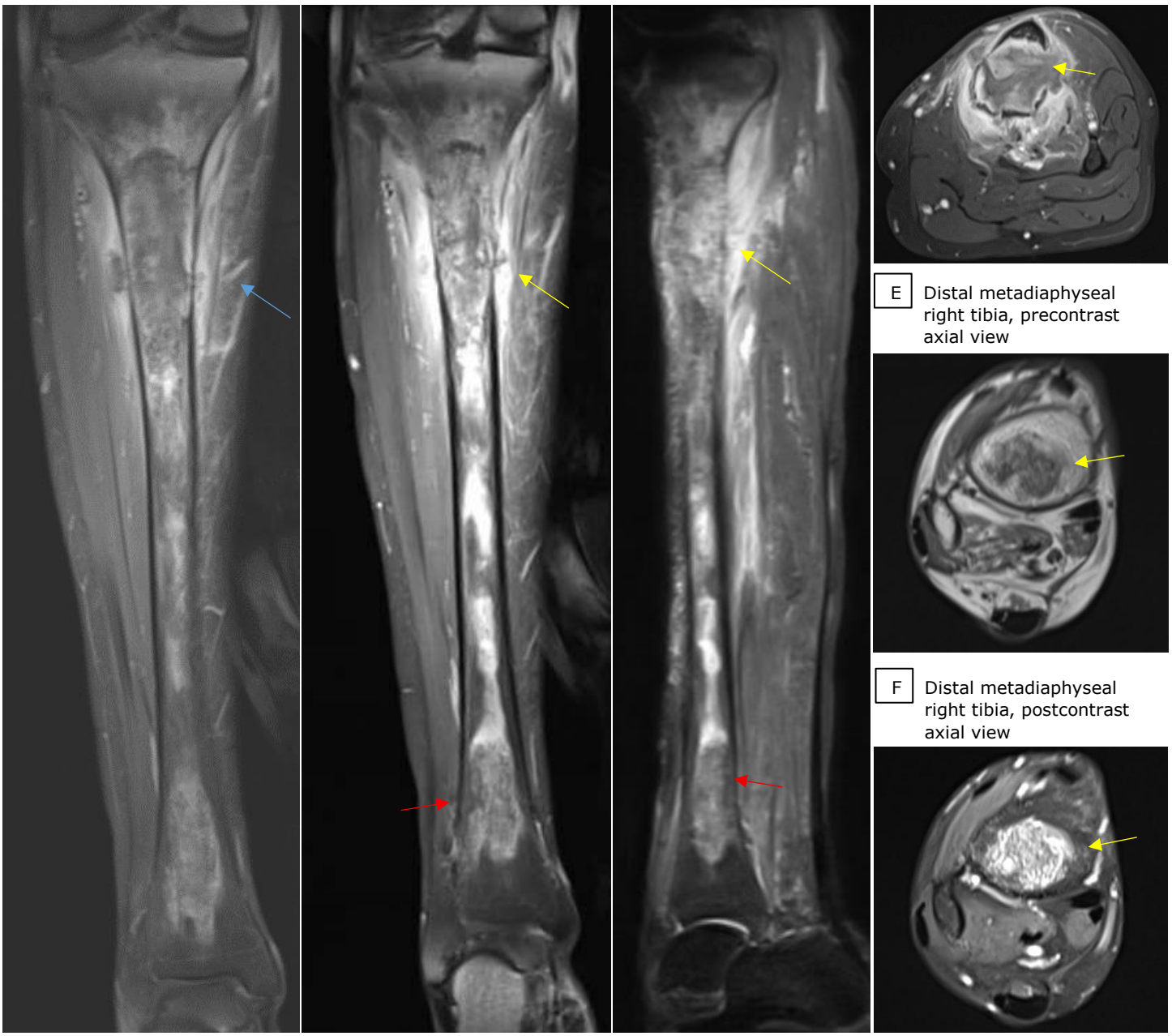
Axial, sagittal, and coronal computed tomography images of the right tibia and fibula show no evidence of a pathologic fracture but do show an aggressive 5-cm lytic lesion with cortical scalloping in the proximal tibial shaft (yellow arrows). There is associated irregular periosteal reaction. The heterogeneous sclerosis in the distal tibial diaphysis that was identified on radiographs (Figure 1) is also shown here (red arrows).

The radiographic pattern and the symmetry of the intramedullary sclerosis, along with corresponding MRI findings, were most consistent with ECD. However, the destructive lytic mass in the proximal right tibia remained undiagnosed. This lesion was biopsied under CT guidance, and pathologic examination revealed neoplastic cells expressing Langerin, S100, *CD1A*, and the *BRAF*^{V600E} variant, with no significant staining for pan-keratin (AE1/AE3) or *CD138* (Figure 4). Following the biopsy, the mass was curetted and cemented, and open reduction and internal fixation (ORIF) was performed. However, the lesion could not be entirely excised due to its friable, coagulated structure. The oncology team was consulted for further treatment options. Positron emission tomography and computed tomography (PET/CT) imaging was ordered for staging, but the patient has not followed up with oncology. She continues to follow up with orthopedic surgery, and at her most recent orthopedic follow-up 16 months after surgery, the patient was ambulating independently and without pain.

Discussion

LCH is a rare multisystem disease with a broad clinical spectrum. It most commonly affects

Figure 3. Magnetic Resonance Imaging (MRI) of the Right Tibia in a 69-Year-Old Woman with Mixed Langerhans Cell Histiocytosis Erdheim-Chester Disease.



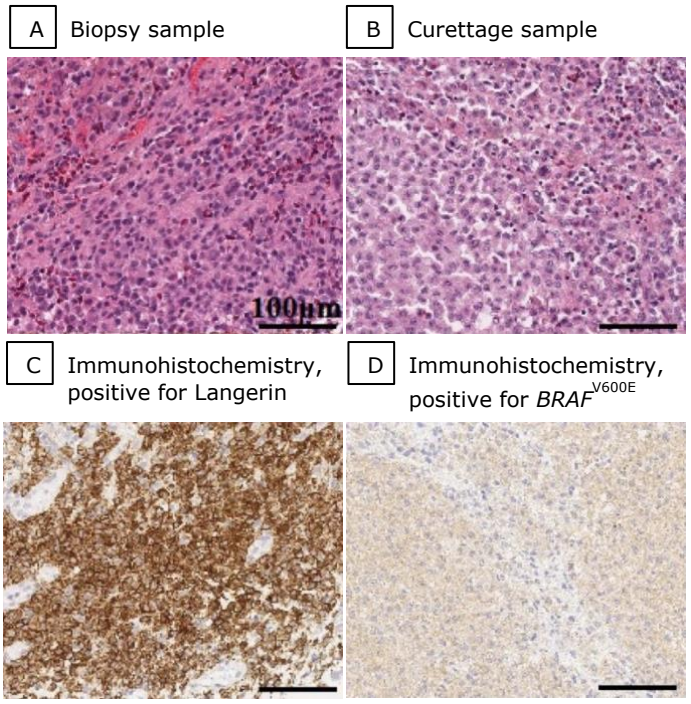
(A) Coronal T1-weighted fat-saturated postcontrast and (D) axial postcontrast T1-weighted MRI of the proximal right tibial lesion demonstrate an aggressive mass measuring 7.4 cm in the proximal tibia with multiple areas of cortical breakthrough and extension into the soft tissues (D, yellow arrow). Note, this lesion measured 4.5 cm on radiographs taken during the same period (Figure 1C, 1D). Imaging on the coronal axis also shows associated myositis and subcutaneous edema (A, blue arrow). There is no joint involvement.

(B) T1-weighted fat-saturated postcontrast and (C) short-TI inversion (STIR) MRI of the right tibia demonstrate an aggressive mass in the proximal tibia (B, C, yellow arrows). Also noted are multifocal STIR hyperintense and enhancing osseous lesions of the distal tibia (B, C, red arrows).

(E) Precontrast T1-weighted and (F) axial T1-weighted fat-saturated postcontrast MRI of the distal metadiaphyseal right tibia demonstrate intrinsically T1-hypointense geographic marrow replacement (E, F, yellow arrows) with heterogeneous enhancement on postcontrast image.

children, but it has also been reported in adults.[3] While LCH can involve multiple organs, it primarily affects the axial skeleton. Imaging features can vary widely, but lytic lesions are a classic radiographic finding. In the long bones, LCH may present with a permeative, aggressive appearance and other destructive characteristics such as periosteal reaction, endosteal scalloping, and associated soft tissue masses.[4] Histologic features of LCH include the presence of Langerhans cells with Birbeck granules when viewed with electron microscopy and the expression of Langerin, *CD1A*, and S100 on immunohistochemistry tests. *BRAF*^{V600E} mutations are commonly identified.[4] The prognosis of LCH varies based on disease extent. Patients with single-system involvement of LCH typically have excellent outcomes, while patients with LCH impacting multiple systems, especially the liver, bone marrow, or spleen, have a poor prognosis.[5]

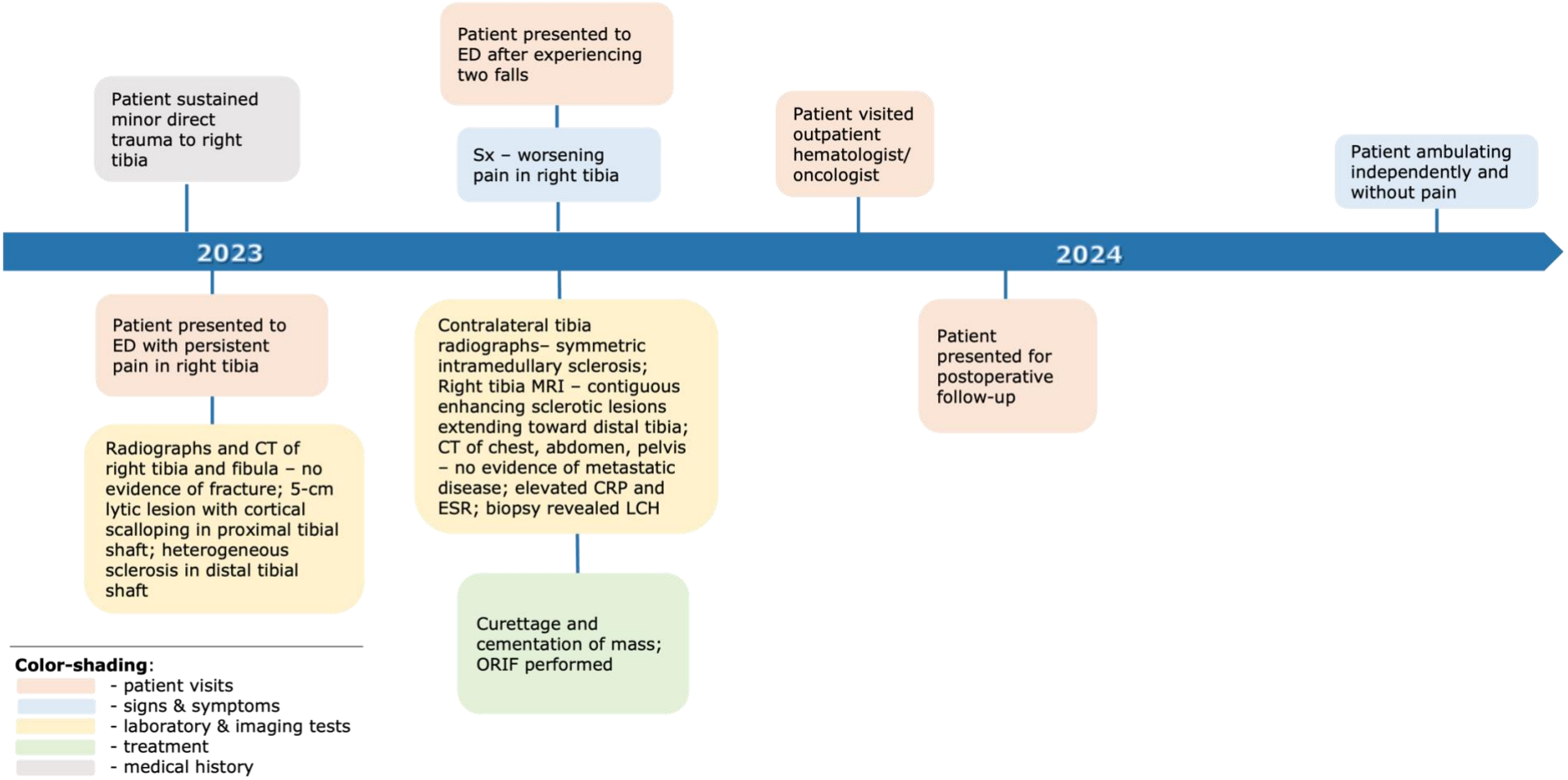
Figure 4. Photomicrographs of Histologic Sections from the Tibia of a 69-Year-Old Woman with Mixed Langerhans Cell Histiocytosis Erdheim-Chester Disease.



(A,B) Histologic sections from the tibial biopsy and curettage specimens showed sheets of epithelioid cells with folded nuclei, nuclear grooves, and eosinophilic cytoplasm with a background of prominent eosinophils.
(C,D) Immunohistochemistry testing of the specimens revealed Langerin and *BRAF*^{V600E} mutant protein. All photomicrographs correspond to 20x magnification, with scale bars indicating 100μm.

ECD is an even rarer condition, with fewer than 1500 cases reported in the literature since it was first described in 1930.[6] Unlike LCH, which primarily affects children, ECD predominantly affects adults in the fifth through seventh decades of life, although rare pediatric cases have been documented.[7] Like LCH, the musculoskeletal system is the most common site of involvement in ECD and is involved in up to 96% of cases.[7] Radiographically, ECD is characterized by symmetric, diffuse, bilateral intramedullary osteosclerosis typically in the metadiaphyseal region of the long bones around the knees, a finding that is pathognomonic for the disease.[8,9] On MRI, ECD lesions in the bone appear as irregular geographic areas of hypointense marrow replacement on T1-weighted imaging, heterogeneous hyperintensity on T2-weighted and STIR images, and enhancement on postcontrast imaging.[10] Although ECD radiographic findings of intramedullary sclerosis typically exclude the epiphyses, MRI may reveal marrow replacement extending into these regions.[10] Histologically, ECD shows foamy histiocytes, sclerosis and fibrosis, and stain positive for *CD68* and *CD163*, negative for Langerin and *CD1A*, and negative to weakly positive for S100.[9] ECD, like LCH, is associated with *BRAF*^{V600E} variants, which are present in the majority of patients with either disease.[1] Like LCH, the prognosis of ECD is variable depending on the extent of disease. Cases involving the lungs or central nervous system have a worse prognosis.[11] While LCH and ECD overlap is an increasingly recognized phenomenon, there is limited discussion of this phenomenon in the radiology literature. To our knowledge, the case presented here is one of the few documented instances in the literature to date. In our case, the proximal destructive lytic lesion in the right tibia was proven through pathologic examination to be LCH. Although the distal lesion was not biopsied, the imaging findings are consistent with ECD, showing concurrent symmetric bilateral intramedullary osteosclerosis in the distal metadiaphyses with enhancement on postcontrast MR images. [8,9] Our case is particularly unique given the directly contiguous appearance of the proximal LCH lesion and distal ECD lesion seen on MRI (Figure 3).

Case report timeline



Abbreviations: CRP, C-reactive protein; CT, computed tomography; ED, emergency department; ESR, erythrocyte sedimentation rate; LCH, Langerhans cell histiocytosis; ORIF, open reduction and internal fixation; Sx, symptoms

Recent literature suggests that LCH and ECD may be more closely related than previously recognized.[12] In 2016, the classification of histiocytosis was updated to consist of five distinct groups: Langerhans group, or "L" group; cutaneous and mucocutaneous group, or "C" group; malignant histiocytosis group, or "M" group; Rosai-Dorfman disease group, or "R" group; and hemophagocytic lymphohistiocytosis group, or "H" group. Under this revised system, ECD and LCH are grouped together within the "L" group, which encompasses LCH, ECD, mixed LCH/ECD, and indeterminate cell histiocytosis (ICH).[12] Understanding the genetic and biochemical similarities, and the potential overlap of "L" group histiocytoses, is important for providing accurate diagnoses when additional screening tests are conducted following the initial diagnosis. Although the patient in this case has not received further workup or treatment, imaging modalities such as technetium-99m bone scintigraphy and PET/CT may prove valuable in identifying other bony lesions that may be occult at the time of the initial diagnosis.[9,10]

Conclusion

This case describes a rare presentation of a pathology-proven LCH lesion with directly contiguous imaging overlap of ECD lesions in the tibia. Awareness of concurrent LCH and ECD lesions can help guide the use of appropriate diagnostic imaging and histopathologic testing.

Author Contributions

Conceptualization, V.G.; Acquisition, analysis, and interpretation of data, W.Q., Z.P., B.E., and V.G.; Writing – original draft preparation, W.Q.; Review and editing, W.Q., Z.P., B.E., V.G.; Supervision, V.G. All listed authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

Disclosures

None to report.

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