



Classic Hodgkin lymphoma with initial extranodal osseous presentation: a case report and literature review

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Abstract: Initial extranodal osseous presentation of Classic Hodgkin lymphoma (CHL) is extremely rare. The present study describes a case of CHL in an 11-year-old male presenting with lower back and right hip pain. Radiologic imaging showed a solitary lytic lesion involving the L5 vertebrae and sacrum. Pathologic examination led to a diagnosis of extranodal osseous CHL and further workup proved bone marrow and nodal disease. Diagnosis of extranodal osseous CHL is challenging, especially in this age group and location. When confronted with a solitary lytic bone lesion in a young patient, more common benign and neoplastic entities enter the differential diagnosis and include osteomyelitis, Langerhans cell histiocytosis, epithelioid hemangioma of bone, leukemia, and anaplastic large cell lymphoma (ALCL) among others, with extranodal osseous CHL being one of the less common entities in the differential diagnosis. This case report raises the awareness of extranodal osseous CHL as one of the entities to consider when confronted with a solitary lytic bone lesion in a young patient.

Keywords: Hodgkin lymphoma; extranodal presentation; lytic bone lesion; bone marrow involvement

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Introduction

Classic Hodgkin lymphoma (CHL) accounts for 95% of all HL cases with bone marrow involvement occurring in 5% of all CHL cases (1). On the other hand, extranodal forms of HL are rare, accounting for <1% of all HL cases with the most common locations being the digestive tract, lungs, central nervous system and bone (2,3).

The initial presentation of classic Hodgkin lymphoma in a pediatric population typically consists of lymphadenopathy, fever, night sweats and weight loss. Extranodal osseous lesions are rarely seen at the time of diagnosis with only a handful of cases described in the literature.

Case presentation

The present study describes a case of HL with initial extranodal osseous presentation in an 11-year-old male. The patient presented with 5 months of severe pain in the lumbar-sacral region with radiation to both lateral areas

of the legs, without any substantial neurological deficits, fever or weight loss. Red blood cell count was normal, and further examination revealed cervical lymphadenopathy. Radiological evaluation detected a lytic lesion in L5 vertebral body and right iliac bone, extending to both psoas muscles (*Figure 1*). Pathological evaluation included biopsy of the L5 lesion (*Figure 2*) which showed a prominent vascular component, scattered Reed-Sternberger (RS) cells with prominent nucleoli, and a heavy eosinophilic infiltrate. The staging bone marrow biopsy showed involvement by HL (*Figure 3*).

Discussion

The Lugano staging system is the most current lymphoma staging classification system which was derived in 2011 from the Cotswolds-modified Ann Arbor classification system. Based on this classification, stage IV is defined as: “diffuse or disseminated involvement of at least one extranodal organ with or without associated lymph node involvement” (4).



Figure 1 MRI of lumbar spine showing a bone marrow infiltrative process involving at least the L5 vertebrae and large part of the sacrum with the extension into the paraspinal soft tissues as well as epidural space and compression on the thecal sac highly suspicious for lymphoma.

Extranodal osseous involvement in Hodgkin lymphoma is uncommon. Even in the late stages only 9% to 35% of cases have any bone involvement, and very rarely at the time of presentation (5) as in our case.

Kumar *et al.* (6) reported a case with a previous diagnosis of Hodgkin lymphoma that was successfully treated, but later presented with a solitary lytic bone lesion in the right upper humerus. Microscopic examination of the biopsy revealed classical binuclear and mononuclear RS cells in a lymphoplasmacytic background with admixed eosinophils, neutrophils and histiocytes. A diagnosis of extranodal osseous Hodgkin lymphoma was made with RS cells staining for CD15 and CD30.

Similar to Kumar *et al.* (6) Li *et al.* (7) and Li *et al.* (8) also reported two cases of extranodal osseous Hodgkin lymphoma who initially presented with a lytic lesion of the rib and sternum respectively.

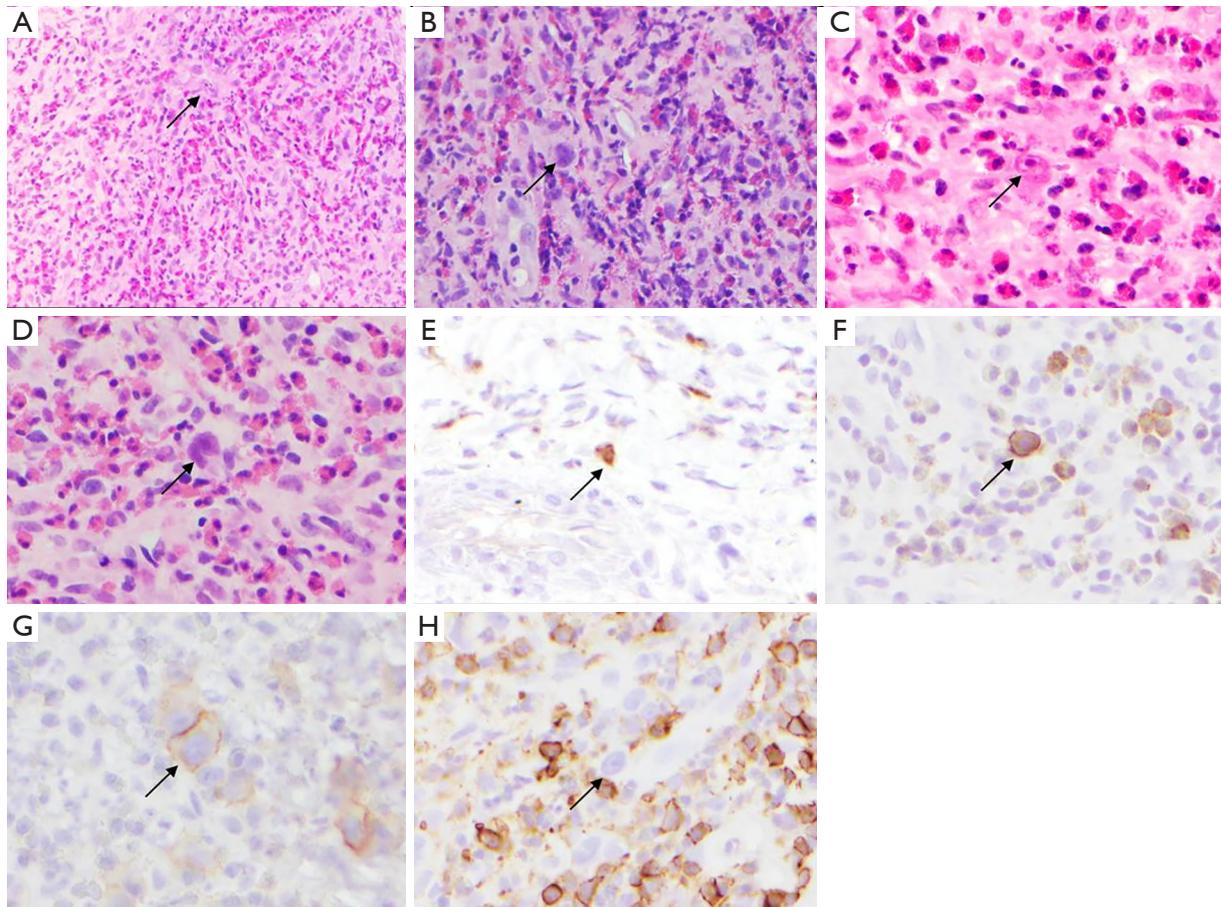


Figure 2 RS cells (arrows) present in a fibrotic and vascular background admixed with abundant eosinophils [(A) H&E, 20 \times ; (B-D) H&E, 40 \times] with positive staining for Pax-5 [(E) 40 \times], CD15 [(F) 40 \times], CD30 [(G) 40 \times] and negative CD45 [(H) 40 \times].

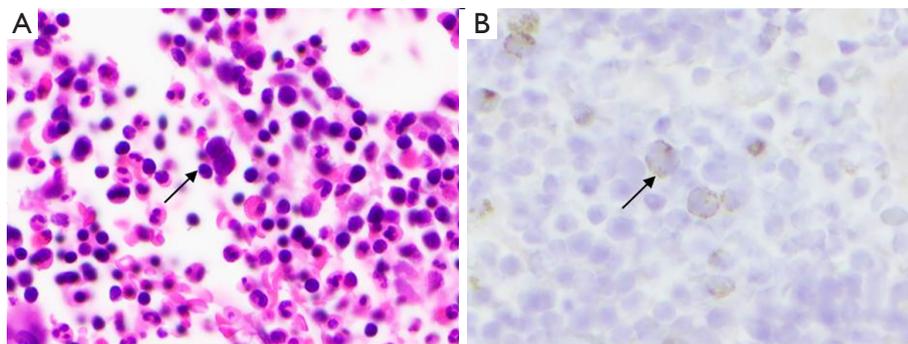


Figure 3 Bone marrow involvement by tumor cells (arrow) [(A) H&E, 100 \times] staining positive for CD30 (arrow) [(B) 100 \times].

In contrast to the cases reported of primary bone lymphoma reported by Kumar *et al.* (6) and Li *et al.* (7) where no other sites of involvement were found, Dogan *et al.* (5) described 49 cases of Hodgkin lymphoma with bone involvement reported at the time of initial diagnosis. The majority of these cases also had lymph nodes and other organ involvement with bone lesions at staging workup. With similar gender distribution, and the most common bones involved were from the axial skeleton: in our case, both right ilium and lumbar vertebrae were involved.

Sidharth *et al.* (9) conducted a study focusing on the pediatric population, whereby they staged 49 first-time-diagnosed patients younger than 18-year-old. Twenty-four percent of these patients presented initially with stage IV (advanced stage) and subsequently showed less satisfactory response to treatment. A much higher percentage was reported in another study by Sherief *et al.* (10) focusing on patients ranging from 3 to 14 years old whereby they noted that more than half of the patients (55.9%) had advanced disease at the time of diagnosis. On the other hand, Gaudio *et al.*'s, (11) study on patients with a median age of 41-year-old reported a percentage of only 8% of patients presenting initially with advanced disease. Based on these studies, there exists a significant difference in the proportion of pediatric versus adult patients presenting with advanced disease.

Radiologically, lytic lesions of bone represent a variety of conditions ranging from benign (including infections and bone cysts) to malignant neoplasms such as multiple myeloma and Hodgkin lymphoma. Based on our patient's young age and radiologic findings the following entities, besides CHL, entered the differential diagnosis: epithelioid hemangioma of bone, Langerhans cell histiocytosis, osteomyelitis, ALCL, mastocytosis, acute myelomonocytic leukemia, and large B cell lymphomas (LBCL) including diffuse LBCL and T-cell/histiocyte-rich LBCL.

Epithelioid hemangioma of bone has been reported most commonly in the tubular bones of the extremities (12). Although recognized as a benign tumor by the WHO, it can display locally aggressive features. It manifests radiologically as an aggressive lytic lesion, usually involving the diaphysis of the long bones, pelvis, and scapula. It also can grow rapidly, with a disproportion between the very large soft tissue mass and the cortical destruction (13). Both Epithelioid hemangioma of bone and extranodal osseous Hodgkin lymphoma may present histologically with a lymphoplasmacytic infiltrate with heavily admixed histiocytic and eosinophilic background, prominent vascular component and reactive fibroblastic proliferation. However, the presence of RS cells determines the diagnosis of CHL. Consequently, a thorough and precise search for RS cells should be performed when encountered with a bone lesion with a richly vascularized mixed inflammatory background.

Langerhans cell histiocytosis also presents as a lytic mass that may possibly extend into soft tissue. Histologically, it shows a background composed of variable admixture of eosinophils, giant cells, neutrophils and Langerhans cells; which are easily distinguished from RS cells by their reniform nuclei, absence of prominent nucleoli and positivity for S100 and CD1a immunostains with absent CD30 staining.

Osteomyelitis may produce focal bone destruction with soft tissue permeation and can present with a heavy eosinophilic and lymphoplasmacytic background inflammation with associated bone destruction and stromal fibrosis; however, it lacks RS cells.

Anaplastic large cell lymphoma (ALCL) is a T cell lymphoma that usually presents in children and young adults, has common extranodal or bone marrow involvement, and is characterized by large hallmark cells with abundant cytoplasm that can have multiple wreath-like

nuclei resembling Reed-Sternberg cells. The hallmark cells are usually positive for CD30, but unlike RS cells, they tend to express CD45, CD43, EMA and ALK (in ALK-positive ALCL) (14).

Although mastocytosis rarely presents as a skeletal disorder, in cases associated with bone marrow infiltration it can manifest as diffuse, poorly demarcated, sclerotic, and lucent areas involving the axial skeleton with associated lytic changes, osteopenia, osteonecrosis and bone destruction (15). Microscopically, mastocytosis presents as perivascular and peritrabecular condensation of compact foci of more than 15 mast cells within fibrohistiocytic matrix with absent RS cells.

Acute myelomonocytic leukemia requires the presence of myeloblasts, monoblasts and promonocytes as 20% or more of the nonerythroid cells in the blood or bone marrow (1). In our case, the patient's CBC was normal and the bone marrow did not show any evidence of blasts.

Diffuse large B cell lymphoma (DLBCL) is more common in adults and is rarely associated with osseous or bone marrow involvement. It usually presents as a diffuse sheet-like proliferation of medium-sized to large lymphoid B-cells (1) some of which may mimic RS cells. Both the anaplastic variant and mediastinal subtype of DLBCL can express CD30; however, unlike RS cells they are usually positive for CD45, CD20, CD79a, CD75, Oct-2 and BOB-1.

T-cell/histiocyte-rich LBCL affects mainly middle-aged men, presents as a nodal disease with common bone marrow involvement, and is characterized by scattered single large B cells mimicking RS cells embedded in a background of small T cells and histiocytes. The large atypical B cells have a different immunophenotype than RS cells and usually express pan-B-cell markers including CD19, CD20, CD79a and Bcl-6 with negative expression for CD15 and CD30 (1).

Given the overlapping morphologic features among the aforementioned entities, the final diagnosis of extranodal osseous Hodgkin lymphoma will depend on the presence of Reed Sternberg cells and their positivity for CD15 and CD30 with negative expression for CD45, CD43, ALK, S100, CD1a and pan-B-cell markers.

In our case, the patient initially presented with a solitary bone lytic lesion of L5 vertebra and sacrum. Microscopic examination of the L5 bone biopsy showed a prominent vascular component, scattered large cells with prominent nucleoli and a heavy eosinophilic infiltrate, which raised the concern of extranodal osseous Hodgkin lymphoma given the patient's age and the presence of cervical lymphadenopathy. Further immunohistochemical workup revealed that the large cells (Reed Sternberg cells)

were positive for CD15, CD30 and Pax-5 supporting the diagnosis of classic Hodgkin lymphoma. Consequently, the patient underwent a bone marrow biopsy which also showed involvement by Hodgkin lymphoma and is currently completing chemotherapy regimen with promising results.

Conclusions

Hodgkin lymphoma presenting initially as a bone lesion is very uncommon and could be misleading, especially in the pediatric population. Clinicians should maintain a high suspicion for hematologic malignancies and pathological examination thorough immunohistochemical workup plays a vital role in establishing this challenging diagnosis.

Acknowledgments

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are 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. The authors have obtained a written consent from the mother.

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