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A case of Primary Bone Anaplastic Large Cell Lymphoma

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Patient: Female, 52
Final Diagnosis: Primary bone anaplastic large cell lymphoma
Symptoms: Bone pain
Medication: —
Clinical Procedure: —
Specialty: Oncology

Objective: Unusual clinical course

Background: Anaplastic large cell lymphoma (ALCL) is a relatively rare subtype of non-Hodgkin's lymphoma (NHL). Like other types of NHL, ALCL primarily involves the nodal area, and sometimes it can involve several extra-nodal sites such as skin, soft tissue, and lungs. However, extensive bone involvement in cases of ALCL is very rare whether it is primary or secondary. Without nodular involvement, ALCL can be misdiagnosed as bone tumor or metastatic carcinoma such as lung, breast, or prostate cancer, which frequently spread to bone.

Case Report: A 52-year-old woman with generalized pain and 2 months of fever of unknown origin presented to our institution. After extensive evaluation, only multiple osteolytic bone lesions with periosteal soft tissue reaction were identified. Repeated core needle biopsy revealed only inflammatory cells with histiocytic reactions. After pathologic and chromosomal analysis of sufficient tissue, which was acquired from incisional biopsy, primary bone ALCL was confirmed.

Conclusions: Clinicians should keep in mind that ALCL can present with extensive bone involvement without nodal involvement.

MeSH Keywords: Fever of Unknown Origin • Lymphoma, Large-Cell, Anaplastic • Osteolysis

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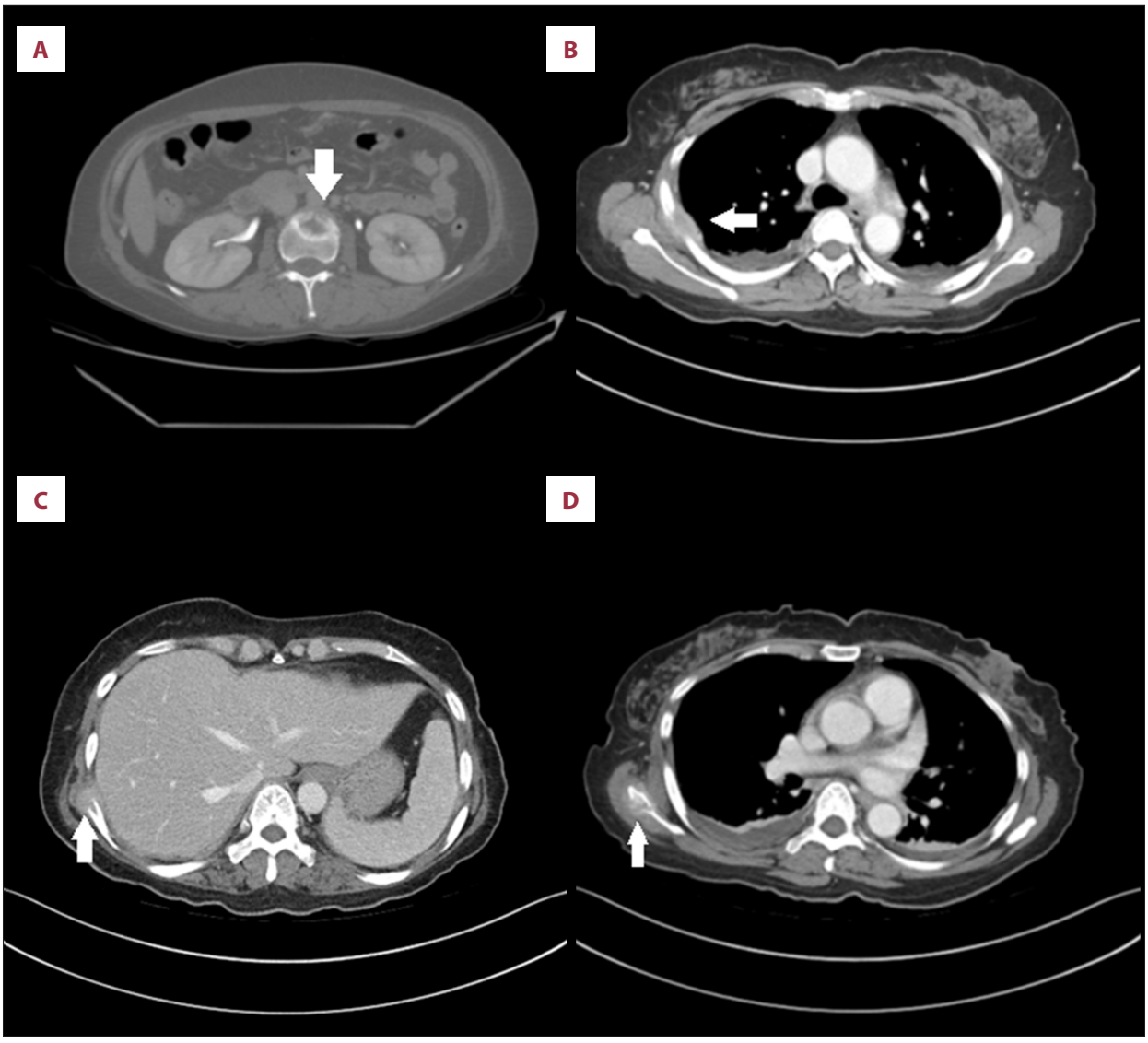
Background

Primary bone lymphoma (PBL) is a very rare disease entity that comprises fewer than 1–2% of all malignant lymphomas and 3–7% of primary bone tumors [1,2]. Therefore, it is rarely considered as a differential diagnosis of malignancy with bone-limited lesions. However, because lymphoma responds to treatment better than other malignancies that can metastasize to bone or primary malignant bone tumor, making an accurate diagnosis is clinically important. Among PBLs, diffuse large B cell lymphoma is reported as the most commonly found (78–97%) histopathological subtype [1,2]. However, other subtypes including NK/T cell lymphoma and anaplastic large cell lymphoma (ALCL) also have been rarely reported, and their rare incidence makes diagnosis more difficult. We would like to call attention to a case of primary bone ALCL.

Case Report

A 52-year-old woman presented with a 2-month history of pain in multiple areas and intermittent fever. Her past medical history was unremarkable except for the above symptoms. Before she presented at our institution, she had been treated for fever of unknown origin (FUO) at another institution. During that period, she received an extensive examination, including blood culture, imaging studies such as abdomen computerized tomography (CT), and echocardiography. However, all the laboratory results were negative except for a high C-reactive protein (CRP) level (175.27 mg/L) and leukocytosis (white blood cell count [WBC] 17,260/μL). On abdomen CT, there were no abnormal lesions except a round osteolytic lesion in the L2 vertebra (Figure 1A). Because in Korea, tuberculosis (TB) osteomyelitis is one of the common causes of FUO in patients with bone lesions and because the patient showed focal pleural thickening,



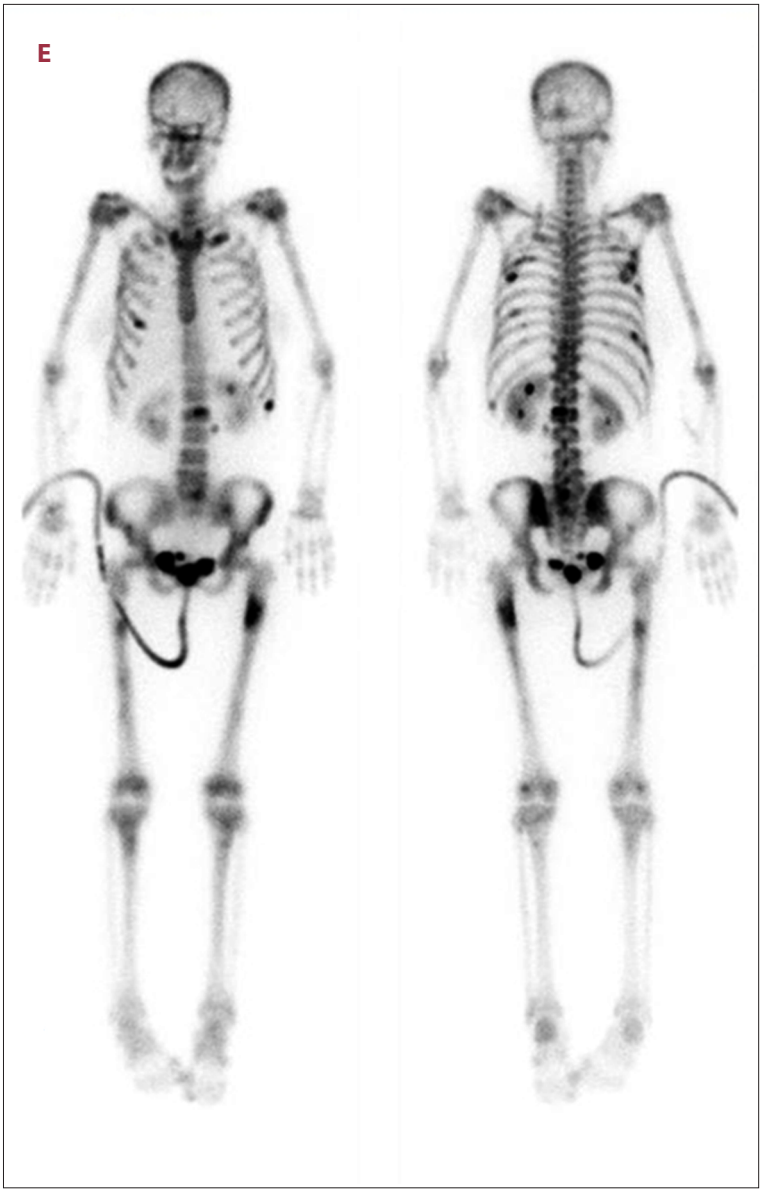


Figure 1. Computed tomography (CT) scan of abdomen shows osteolytic lesion in L2 spine (**A**) (arrow). Sequentially performed chest CT shows additional osteolytic lesions on the right 4th rib (**B**), 9th rib (**C**), and scapula (**D**) (arrow). On whole body bone scan, there are multiple metastatic skeletal hot uptake foci involving ribs on both sides, L2 vertebra, both proximal femurs, and both sacroiliac joint-forming bones (**E**).

she received 2 weeks of anti-TB medication for the diagnostic trial and received the QuantiFERON-TB test. However, her fever and other symptoms did not improve, and the result of the QuantiFERON-TB test was negative. Therefore, she stopped the anti-TB medication and was transferred to our institution. Physical examination showed no palpable lymph nodes, organomegaly, or cutaneous lesions. The patient's WBC was 16,540/μL (normal range: 5,000–10,000/μL), hemoglobin level was 9.7 g/dL (normal range: 14–18 g/dL), and platelet count was 400,000/mm^3 (normal range: 150,000–450,000/mm^3). Renal function test results and liver enzyme levels were within normal range. Alkaline phosphatase was 422 IU/L (normal range: 104–338 IU/L), and γ-glutamyl transpeptidase was 75 IU/L (normal range: 9–64 IU/L). Calcium and phosphorus were 7.8 mg/dL (normal range: 8.1–10.6 mg/dL) and 3.5 mg/dL (normal range: 2.5–4.5 mg/dL), respectively. Serum total protein and albumin were 6.9 g/dL (normal range: 6.6–8.3 g/dL) and 3.11 g/dL (normal range: 3.5–5.2 g/dL), respectively. Lactate dehydrogenase (LDH) was 249 IU/L (normal range: 208–378 IU/L). Electrophoresis/immuno-fixation electrophoresis of serum protein revealed no specific abnormality. HIV test was negative. However, follow-up abdomen and chest CT, which were performed one month after initial CT, revealed newly developed osteolytic lesions in the right 4th and 9th ribs, right scapula, and sacrum with periosteal soft tissue swelling (Figure 1B–1D). However, still there was no definite mass-forming lesion or lymph node enlargement, which can be a clue to the primary origin of a malignancy. Whole body bone scan with technetium-99 showed multiple hot spots in multiple ribs, right scapula, L2 vertebra, sacrum, and both proximal

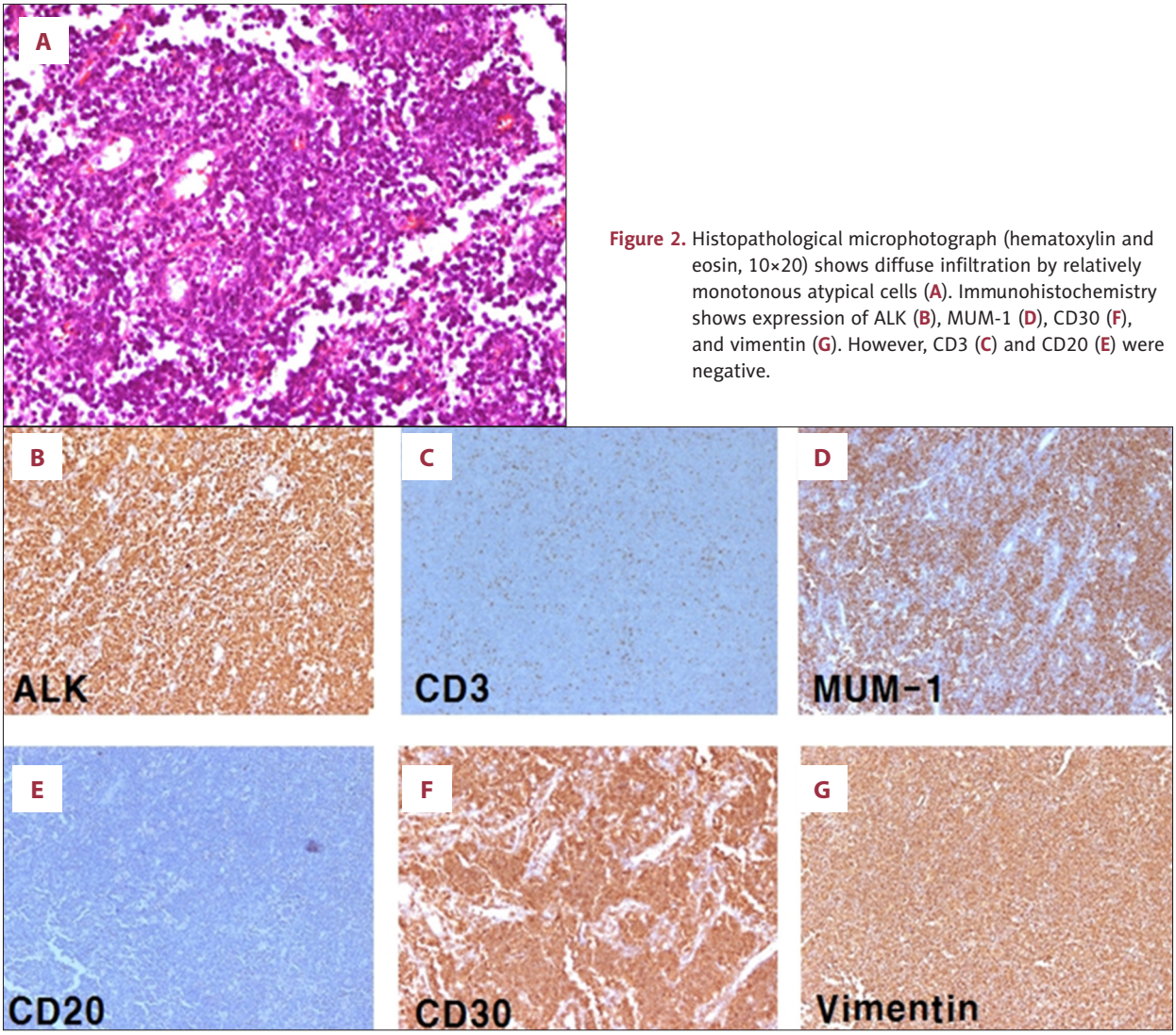


Figure 2. Histopathological microphotograph (hematoxylin and eosin, 10×20) shows diffuse infiltration by relatively monotonous atypical cells (**A**). Immunohistochemistry shows expression of ALK (**B**), MUM-1 (**D**), CD30 (**F**), and vimentin (**G**). However, CD3 (**C**) and CD20 (**E**) were negative.

femurs (Figure 1E). On positron emission tomography (PET)-CT, increased ^{18}F-fluorodeoxyglucose (FDG) uptake was identified on the same lesions with osteolytic bone lesions. However, repeated CT-guided core needle bone biopsies performed on the rib and sacrum with osteolytic lesions were non-diagnostic, revealing only inflammatory cells with reactive lymphocyte and diffuse histiocytic infiltration. Even after extensive immunohistochemical stain (IHC) including pancytokeratin, CD68, CD1a, S-100, vimentin, CD3, CD8, CD20, leukocyte common antigen, CD138, and IgG4, an accurate diagnosis other than acute and chronic inflammation could not be obtained. Finally, a third incisional biopsy on soft tissue around an involved rib (selected as a site based on PET-CT findings) showed diffuse infiltration of anaplastic cells (Figure 2A). At this time, the IHC study including CD30 was helpful to make a diagnosis of primary bone ALCL (Figure 2B–2G). In addition, on the fluorescence *in situ* hybridization study, t(2;5) translocation was demonstrated. Based on the results, a diagnosis of ALK-positive ALCL with prominent bone involvement was made. Because the patient already had disseminated bone lesions, we did not perform additional bone marrow biopsy for staging workup. After diagnosis, she received CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy and showed a complete response after six cycles of chemotherapy. She has been receiving regular follow-up without recurrence for 5 months.

Discussion

Usually ALCL is pathologically characterized by anaplastic and pleomorphic large neoplastic cells that preferentially involve the lymph nodes. Although occasionally multiple bone involvement of ALCL is found in patients with extensive nodal disease, isolated bone involvement by ALCL without lymphadenopathy is very rare. In clinical practice, multiple osteolytic lesions usually remind physicians of metastatic carcinoma or multiple

myeloma rather than lymphoma. Furthermore, less common variants of ALCL such as monomorphic variant or lymphohistiocytic variants make accurate diagnosis more difficult even after pathologic evaluation [3,4]. Therefore, this rare presentation of ALCL can mislead physicians to the wrong diagnosis or delay the accurate diagnosis. Until now, more than 30 cases of primary bone ALCL have been reported [5–12]. Based on those studies, a majority of the previously reported cases had a difficult diagnosis process. Clinically, they were frequently confused with small round cell tumor, metastatic carcinoma, multiple myeloma, and osteomyelitis [5–8], including TB, which can cause lytic bone lesions. Some cases were misdiagnosed as osteomyelitis even after pathologic evaluation [7]. In most of the cases, bone marrow biopsy and trephine biopsy also were negative. Therefore, to avoid delay of diagnosis of primary bone ALCL, some authors emphasized the importance of meticulous histologic examination with early biopsies and recommended that a biopsy specimen be obtained from the involved soft tissue rather than bony tissue because the de-calcification process of bony tissue for further preparation could affect the results of an IHC study [6,7].

After thorough review of literature published in PUBMED, we figured out a few additional clinical tips that can be helpful for suspicion of primary bone ALCL. A clinical aspect is that many of the reported patients were in their teens and twenties. With respect to radiologic findings, many cases showed a characteristic moth-eaten pattern of bone destruction, which is explained because the tumor arises within the intramedullary cavity [13]. In addition, bone lesions were accompanied by an aggressive periosteal reaction, and pathologic confirmation was usually made by biopsy from the periosteal soft tissue.

Also in our case, osteomyelitis was initially suspected as a possible clinical diagnosis. In particular, the normal LDH level and pathologic result from initial needle biopsy worsened the confusion. Even after the initial two pathologic studies, histiocyte-dominant inflammatory cells around tumor cells made accurate diagnosis difficult. But then, intense FDG uptake in involved lesions on PET-CT was helpful to decide on a repeated biopsy and to find an appropriate biopsy site [10]. Eventually, repeated biopsy with a chromosomal study detecting t(2;5) translocation enabled the correct diagnosis.

ALK-positive ALCL and cutaneous ALCL are usually known to have a favorable prognosis. But in case of primary bone ALCL, there is no consensus about prognosis, although many previous case reports insisted that predominant bone involvement by ALCL could be related to poor prognosis irrespective of ALK positivity [5,6]. Further studies investigating clinical behavior and pathogenesis of ALCL according to the involved anatomical sites are warranted.

Conclusions

Clinicians should keep in mind that ALCL can present with extensive bone involvement without nodal involvement, and lymphoma should be considered in differential diagnosis of primary bone lesions. For an accurate and prompt diagnosis, aggressive pathologic evaluation with chromosomal analysis is recommended.

Statement

The authors state that they have no conflict of interest.

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