Primary Bone ALK Positive Anaplastic Large- cell Lymphoma: A Case Report

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Case report

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Abstract

Background: Primary bone lymphoma (PBL) is an uncommon extranodal disease that represents approximately 1-3% of lymphomas. ALK positive anaplastic large-cell lymphoma (ALCL) is an extremely rare type of PBL. The aim of this report is describe the symptoms, diagnosis and treatment of primary bone ALK-positive ALCL.

Case presentation:A 66-year-old man presented with neck and shoulder pain and intermittent fever that lasted for one month to our hospital.After extensive evaluation, positron emission tomography (PET)-CT examination showed multiple osteolytic bone lesions without other sites lesions. CT-guided biopsy of the T10 vertebral body was performed, and the pathology results showed neoplastic cells were positive for ALK-1, CD30 and CD3. A diagnosis of primary bone ALK positive ALCL was ultimately made. The patient received four cycles of CHOP chemotherapy , and we planned to repeat the biopsy and radiological examination after completion of the fifth cycle of therapy.

Conclusions: Primary bone ALK positive anaplastic large cell lymphoma is a rare disease and physicians should keep in mind that ALCL can present with isolated osseous involvement without nodal involvement, and lymphoma should be considered in the differential diagnosis of primary bone lesions.

Background

Anaplastic large-cell lymphomas (ALCLs) are a subgroup of peripheral T-cell lymphomas (PTCLs) thought to be derived from cytotoxic T cells. The 2016 revised World Health Organization (WHO) lymphoma classification recognizes four different entities: systemic ALK-positive ALCL (ALK + ALCL), systemic ALK-negative ALCL (ALK- ALCL), primary cutaneous ALCL (pC-ALCL), and breast implant-associated ALCL (BI-ALCL). Anaplastic lymphoma kinase (ALK) expression has been considered an important favorable prognostic factor for ALCL. ALK positive ALCL represents approximately 3% of adult non-Hodgkin's lymphomas (NHLs) and 10%-15% of childhood lymphomas[1]. ALCL mostly affects lymph nodes, while the involvement of extranodal sites, including the soft tissue, bone, lung and liver, is uncommon[2, 3].

Primary bone lymphoma (PBL) is a subtype of lymphoma that exclusively affects skeletal tissue. The prevalence of PBL is estimated to be 3%-7% among primary bone tumors and less than 2% among all lymphomas in adults[4, 5]. Among PBLs, diffuse large B-cell lymphoma (DLBCL) is the most common pathological type, accounting for approximately70%-80% of all PBLs[6–9]. The ALCL subtype of PBL is extremely rare (3%-5% of all PBLs)[10–13], and it therefore remains unclear whether it is similar to ALCL in general or whether it is a subtype with unique clinical biological characteristics. Furthermore, the prognostic impact of ALK expression in ALCL with primary bone lesions is still under debate.

Due to the rarity of this disease, more relevant studies and case reports are needed. Herein, we report one rare case of primary bone ALK positive ALCL in a 66-year-old male.

Case Presentation

A 66-year-old man presented with a 1-month history of neck and shoulder pain and intermittent fevers. His fevers had no clear pattern in timing or duration. His neck and shoulder pain was not sharp, with no neck and shoulder stiffness or limited movement and was relieved by nonsteroidal antiinflammatory drugs (NSAIDs). He reported a body weight loss of 5 kg in the past month and denied having night sweats, diarrhea, emesis, or appetite changes. His past medical history included diabetes and cervical spondylosis, and there was no family history of malignancy. The patient had taken cefuroxime for 3 days by himself without advice from the doctor. However, intermittent fevers of 37.7 °C-38.9 °C persisted. Therefore, the patient was admitted to a local community hospital and accepted 1 week of hospitalization. Pertinent initial labs included leukocytosis (12.71×10^9/L, 80.2% neutrophils),elevated C-reactive protein (CRP: 115.8 mg/L),elevated alanine aminotransferase (ALT: 82 U/L), elevated aspartate aminotransferase (AST: 61 U/L), elevated lactate dehydrogenase (LDH: 249 U/L)and hypoproteinemia (albumin: 34 g/L). Urinalysis demonstrated trace protein and blood, with negative blood and urine cultures. A cervical magnetic resonance imaging (MRI) plain scan revealed cervical degenerative changes, and chest computed tomography (CT) showed infectious lesions in the upper lobe of the left lung. His primary care doctor suspected lung infection and administered empirical antimicrobial therapy with moxifloxacin for 5 days. His temperature returned to normal and discharged. However, two days after leaving the hospital, the fever (up to 38.8 °C) returned, and his neck and shoulder pain were more worsen ,thus he was transferred to our hospital for further evaluation.

After extensive evaluation, physical examination showed no palpable lymph nodes, organomegaly, or cutaneous lesions. Our blood laboratory results were as follows: leukocytosis (14.39×10^9/L, 84.4% neutrophils), elevated CRP(126.3 mg/L), elevated transaminases (ALT:71 U/L, AST:51 U/L), elevated alkaline phosphatase (208 U/L), elevated LDH (313 U/L) and hypoproteinemia (32.5 g/L).The anti-Epstein-Barr virus (EBV) capsid antigen IgG test was positive, and the tuberculosis antibody tests and tubercle-specific immune responses were also negative. Urinalysis indicated 1 + protein, moderate blood (61 RBCs) and trace leukocyte esterase (10 WBCs/HPF). Blood and urine cultures were negative. Electrocardiogram, serum protein electrophoresis, tumor markers, as well as abdomen and heart ultrasonography were normal. The trephine bone marrow biopsy showed hypocellularity,and the aspirate revealed granulocyte hyperplasia but no cellular atypia. Flow cytometry was negative for any atypical lymphocytes. Chest CT scan revealed local bronchiectasis in the upper left and right middle lobes, furthermore, the obviously osteolytic lesion in T10 vertebral body were also noted(Fig. 1).Because of neck and shoulder pain, a thoracic enhanced MRI was performed. It indicated T2 and T10 vertebrae bone destruction, suggesting evident malignancy (Fig. 2, panels a-b). Based on these findings, he underwent a positron emission tomography (PET)-CT examination for further evaluation. On PET-CT, increased ^{18}F-fluorodeoxyglucose (FDG) avidity involved the left sphenoid wing, the C4-5, T2, T10, L5, S1, and S5 vertebrae, the right humeral head, both sides of the humerus,the right proximal femur. These lesions were identified as hypermetabolic lesions with a maximum standard uptake value (SUV) of 18.64. Different degrees of bone destruction could be observed in corresponding sites, indicating lymphoma or multiple

myeloma involvement (Fig. 2, panels c-f). No lymph node or extranodal site (such as lung, liver, spleen, etc.) lesion was identified. CT-guided biopsy of the T10 vertebral body was performed and the pathological diagnosis was ALCL. Microscopic examination showed the lesions vertebral body were infiltrated by pleomorphic tumor cells which have a scanty cytoplasm and hyperchromatic nucle.The neoplastic cells exhibit small-to medium-sized with irregular nuclei and abundant clear cytoplasm.Hallmark cells (horseshoe-shaped or doughnut cells) are present and Reed-Sternberg cell-like cell were also noted(Fig. 3, panels a-b). Immunohistochemistry showed the large atypical cells were positive expression of ALK (Fig. 3, panel c), CD3 (Fig. 3, panel d), CD30 (Fig. 3, panel e), as well as negative expression of CD2,CD5, CD7, CD4, CD8, CD10, CD19, CD79a, B-cell lymphoma-2, multiple myeloma-1, epithelial membrane antigen and pan-cytokeratin. The proliferative index (Ki-67) was approximately 60% (Fig. 3, panel f). Based on the above findings, the final diagnosis was made as primary bone ALCL, ALK-positive, stage IVB. The patient had already received four cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy, and we planned to repeat the biopsy and radiological examination after completion of the fifth cycle of therapy.

Discussion And Conclusions

PBL is an uncommon extranodal disease that represents approximately 1–3% of the of lymphoma cases and is more common in males than in females (8:1). In 1928, Oberling first described it as reticulum cell sarcoma[14]. Based on their series in 1939, Parker and Jackson[15] established PBL as a distinct clinical entity. According to the last version of the WHO classification of tumors of soft tissue and bone, PBL is defined as a neoplasm composed of malignant lymphoid cells, producing one or more masses within the bone, without regional lymph node or distant extranodal involvement[16].

It is difficult to diagnose PBL by clinical manifestations and common laboratory examination. Pain (82–92%) and swelling (34–45%) of the involved site are two of the most common clinical manifestations of PBL[8],.Other less common presentations include pathological fractures and systemic “B-type” symptoms such as fevers, weight loss, and night sweats. It can involve any skeletal site, and the axial skeleton is the most commonly involved site. PBL most commonly presents as osteolytic or osteoblastic lesions with disease involvement of the cortex and reactive periosteal changes[17]. Plain X-ray films are the initial diagnostic test of choice, but they often underestimate the extent of the lesion. CT scans are useful for disease staging and delineating spinal lesions. MRI is helpful in demonstrating bone marrow and soft tissue involvement. In addition, the functional assessment of bone lesions using FDG-PET imaging plays an important role. Studies have shown that FDG-PET displays a higher specificity and sensitivity than conventional bone scintigraphy in identifying lymphomatous infiltration of skeletal tissue[18].

Among the multiple testing modalities, bone biopsy and immunohistochemical studies remain essential for confirmation of PBL and for differential diagnosis. CT-guided percutaneous biopsy has proven to be a safe and reliable way to obtain sufficient samples[19, 20]. Microscopically, DLBCL is the most common histological subtype of lymphoma with primary or secondary skeletal involvement. It accounts for 70–

80% of all bone lymphomas[6–9], with rare to anecdotal occurrences of follicular, marginal zone, lymphoplasmacytic, anaplastic large-cell, natural killer/T-cell, Burkitt, and Hodgkin lymphomas[21, 22] .Available data on primary bone ALCLs are currently rare. ALCLs with primary bone involvement fulfill the previously mentioned PBL definition and show the typical immunohistochemical and molecular findings noted in a few case reports in the literature. The main differential considerations of PBL include secondary osseous lymphoma, other subtypes of lymphoma (DLBCL, NK/T-cell lymphoma, Burkitt's, follicular and lymphoplasmacytic)[23], osteosarcoma, metastases, Ewing sarcoma[24], chronic osteomyelitis and granulomatous infection such as tuberculosis[25].

The prognosis of patients with primary bone DLBCL is directly correlated with the stage of disease. The 5-year overall survival (OS) varies from 82% for patients with stage IE disease to 38% for patients with disseminated DLBCL with skeletal involvement. However, the prognosis of ALCL-type PBLs is controversial. Noh et al[26] collected twenty-two cases of ALCL with primary bone involvement and found that the ALCL type of PBL showed poor biological behavior compared with PBL (5-year OS was 43.1% and 62–76%, respectively). In addition, the expression of ALK-1 protein has been reported to be a favorable prognostic factor in conventional nodal ALCL, but Nagasaka et al[27] showed that ALK-1 positivity is not a favorable prognostic feature for patients with primary bone ALCL. Therefore, further studies investigating the clinical behavior and pathogenesis of primary bone ALCL are warranted.

Strategies such as chemotherapy, immunotherapy, surgery and radiotherapy have been used to treat primary bone ALCL, yet CHOP remains the most commonly used initial therapy. The addition of etoposide to CHOP (also known as CHOEP) improved outcomes for younger patients with ALK + ALCL (especially those with normal LDH levels at diagnosis) in a large retrospective meta-analysis ($P < 0.04$); however, the regimen was too toxic for older patients[28]. The infusional dose-adjusted etoposide, cyclophosphamide, doxorubicin, vincristine, and prednisone (EPOCH) protocol produced very encouraging outcomes in a single institution long-term prospective study that enrolled ALCL patients with high-risk features. After a median follow-up of more than 12 years, median survival for both ALK + and ALK- patients was not reached, with a 10-year OS rate of 75%[29]. On the basis of these results, CHOEP should be considered in younger patients with ALK + ALCL for initial therapy, while CHOP and da-EPOCH should be reserved for older or less fit patients.

Recently, novel agents have emerged in the treatment of ALCL. Brentuximab vedotin (BV) is an anti-CD30 antibody-drug conjugate that selectively delivers an antimicrotubule agent, monomethyl auristatin E, into CD30-expressing cells. The initial phase 1 study conducted in patients with CD30-positive lymphomas, including ALCL, showed that BV treatment led to a response rate of 38%, including 11 complete remissions. The two patients with ALCL in the study achieved complete remission[30]. Subsequently, a phase 2 study in relapsed/refractory ALCL demonstrated an overall response rate of 86% and complete response (CR) rate of 57%. The median progression-free survival (PFS) was 13.3 months[31]. On the basis of these results, BV has been FDA-approved for relapsed/refractory ALCL following first-line therapy. ALK inhibitors are also very promising because ALK tyrosine kinase activity is essential to the survival of ALK

+ ALCL cells. The oral ALK inhibitor crizotinib has demonstrated activity[32, 33]. Crizotinib, an orally available dual ALK/MET inhibitor currently approved for advanced ALK + non-small-cell lung cancer (NSCLC) in adults, has been shown to induce high response rates: in a case series of nine patients with relapsed/refractory ALK + ALCL, all nine attained a CR following treatment with crizotinib[33]. The duration of response exceeded 30 months in some patients. With the constant development of novel agents, there may be profound modifications in the therapeutic strategies for ALCL in the near future.

In summary, a rare case of primary bone ALK-positive ALCL is reported in this study. Physicians should keep in mind that ALCL can present with isolated osseous involvement without nodal involvement, and lymphoma should be considered in the differential diagnosis of primary bone lesions. For an accurate and prompt diagnosis, clinical features, PET-CT images, pathological histology and immunophenotype should all be considered.

Abbreviations

ALCL: Anaplastic large cell lymphoma;PBL:Primary bone lymphoma;ALK: Anaplastic lymphoma kinase; NHL:non-Hodgkin's lymphoma;DLBCL:diffuse large B-cell lymphoma;NSAIDs: nonsteroidal antiinflammatory drugs; CRP: C-reactive protein; ALT:alanine aminotransferase;AST:aspartate aminotransferase; LDH:lactate dehydrogenase;EBV: Epstein-Barr virus; CT :Computed tomography; PET:Positron emission tomography; FDG: 18F-fluorodeoxyglucose; SUV: Standard uptake value; OS:overall survival; BV:Brentuximab vedotin;CR:complete response; PFS:progression-free survival.

Declarations

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Author Contributions

ZW designed the report and wrote the paper; H TC ,W WH and W QQ collected the patient's clinical data; H YC, YY, Y QQ and CMJ analyzed the data, H HJ and PHY revised the paper; all authors have read and approved the final version of this manuscript.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Zhejiang Provincial People's Hospital (Hangzhou, China).No institutional approval was required to publish the case details.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from

the corresponding author on reasonable request.

Consent for publication

Written informed consent was obtained from the patient for publication of

this case report and accompanying images. A copy of the written consent is

available for review by the Editors-in-Chief of this journal.

Competing interests

Not applicable.

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Figures

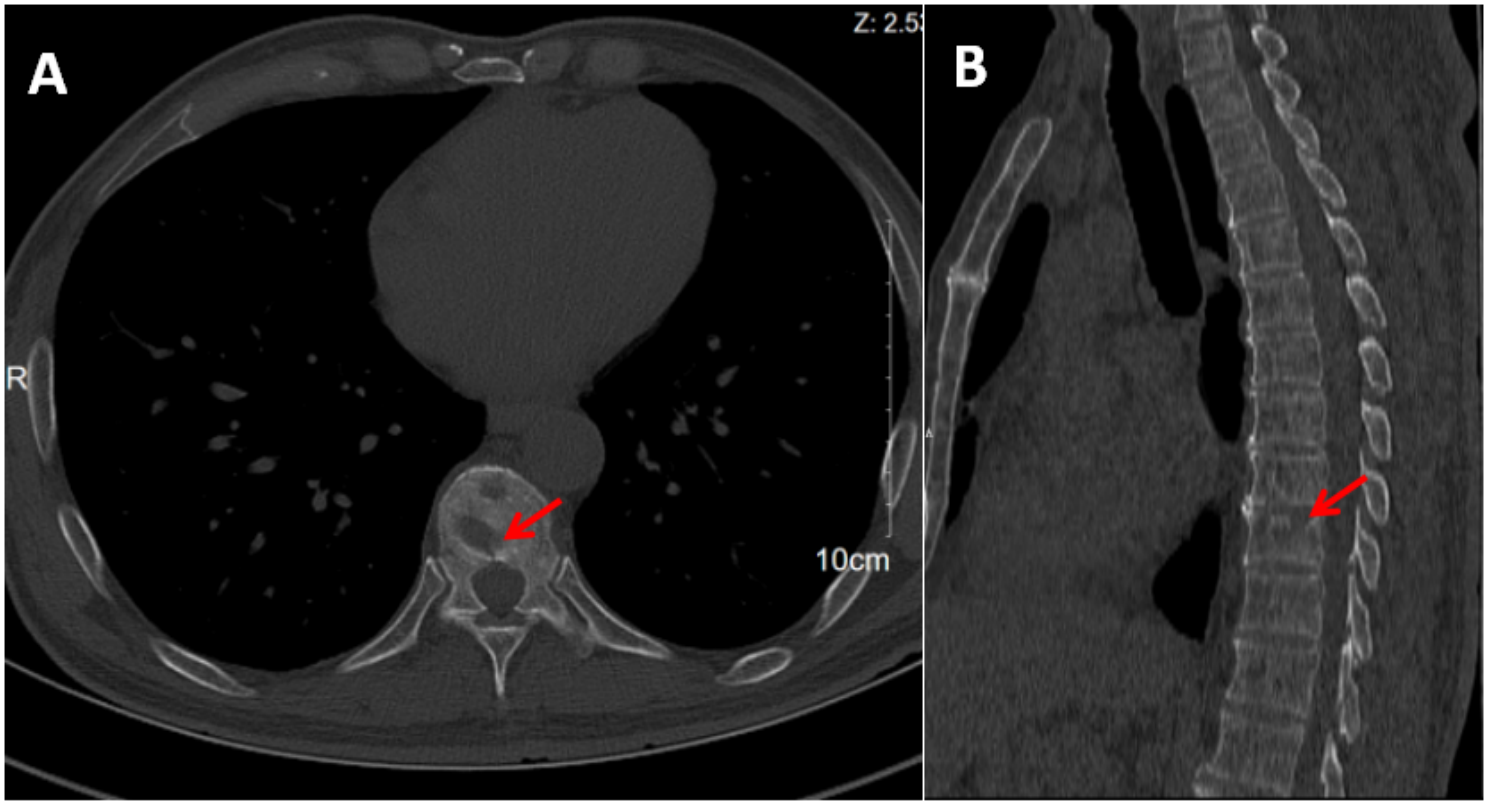

Figure 1

Computed tomography (CT) scan of chest shows osteolytic lesion in T10 vertebral body (A&B) (red arrow).

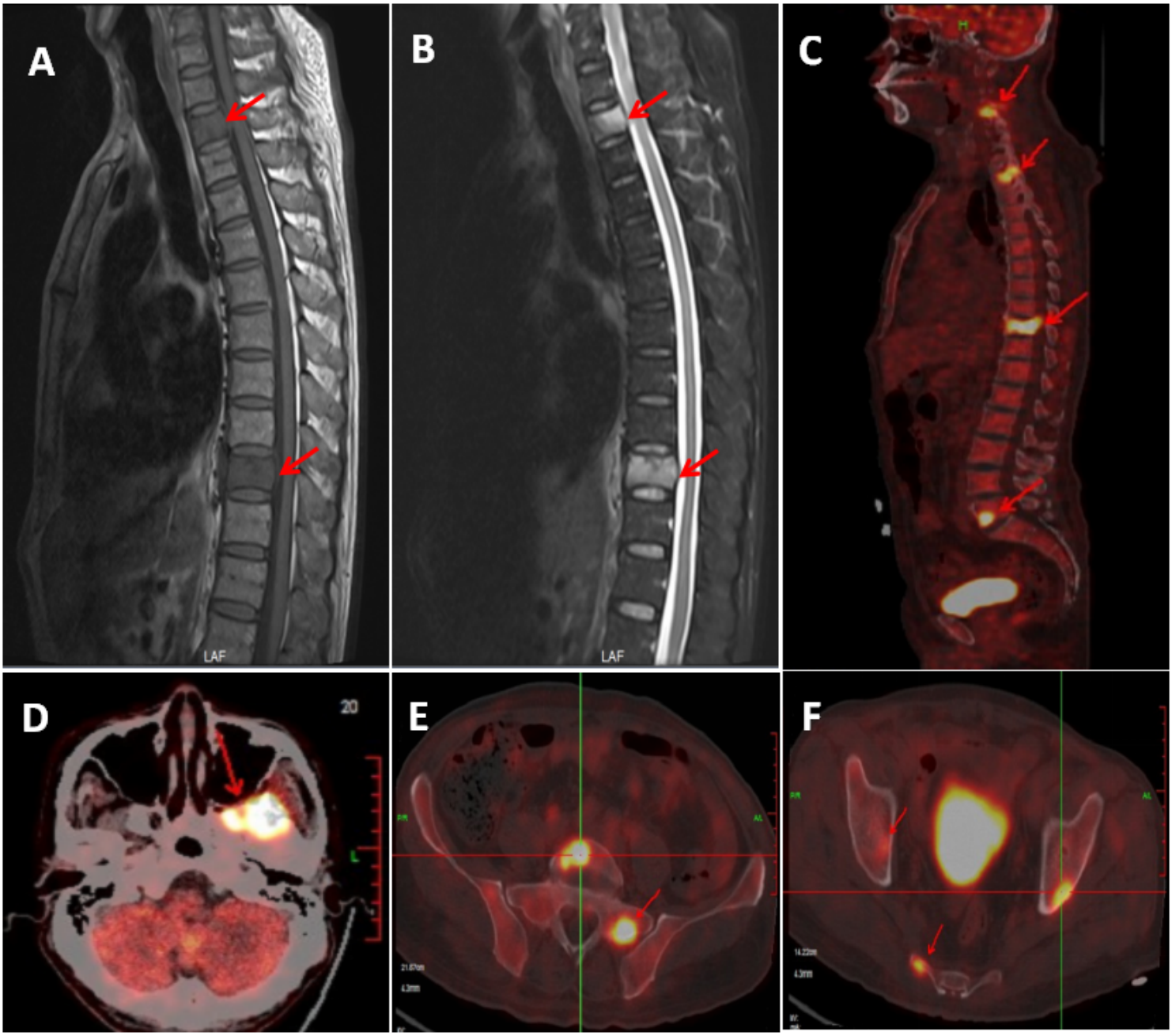

Figure 2

(panels a-b).Thoracic enhanced MRI showed obvious T2 and T10 vertebral bone destruction (red arrows). (panels c-f) .PET-CT showed increased 18F-fluorodeoxyglucose (FDG) avidity involving the left sphenoid wing,the C4-5, T2, T10, L5, S1, and S5 vertebrae; the right humeral head, both sides of the humerus; and the right proximal femur. Multiple osteolytic lesions were identified as hypermetabolic lesions with a maximum standard uptake value (SUV) of 18.64; different degrees of bone destruction can be observed in corresponding sites (red arrows).

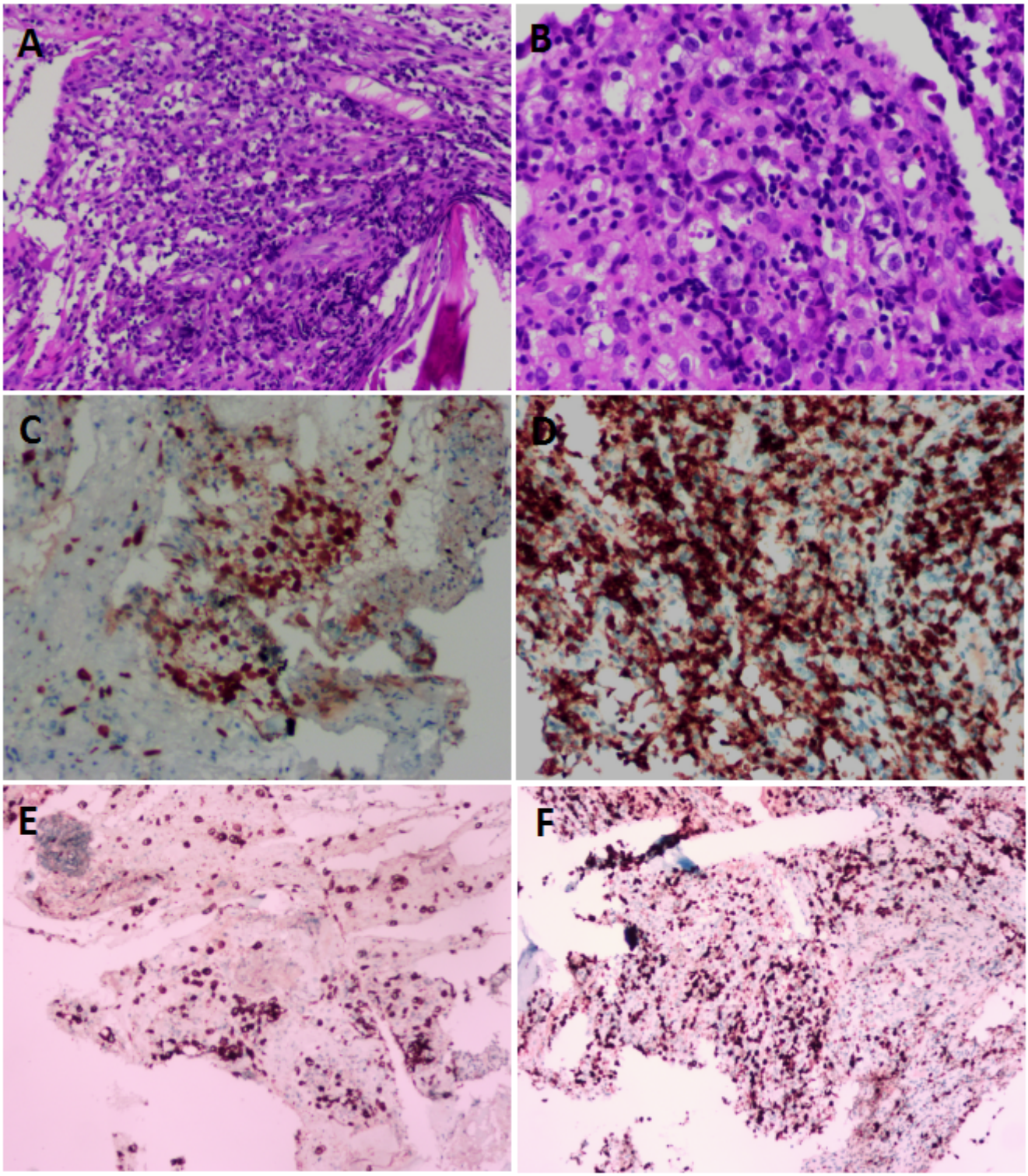

Figure 3

(Panels a-f).Histopathological microphotograph of primary bone anaplastic large-cell lymphoma: Panel a.The lesions vertebral body were infiltrated by pleomorphic tumor cells which have a scanty cytoplasm and hyperchromatic nuclei(magnification x100).Panel b.The neoplastic cells exhibit small-to medium-sized with irregular nuclei and abundant clear cytoplasm.Hallmark cells (horseshoe-shaped or doughnut cells) are present and Reed-Sternberg cell-like cell were also noted(magnification x400).On

immunohistochemistry, the large atypical cells showed positive expression of ALK (Panel c), CD3(Panel d),CD30(Panel e);Ki67 staining showed almost 60 % proliferation index(Panel f).