CASE REPORT

Anaplastic large cell lymphoma masquerading as osteomyelitis of the shoulder: an uncommon presentation

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SUMMARY

The presentation of anaplastic lymphoma kinase protein (ALK)-negative anaplastic large cell lymphoma (ALCL) in bone is rare. We describe a patient with ALK-negative ALCL presenting with clinical and radiographic findings suggesting osteomyelitis 6 months after left rotator cuff repair surgery. A review of the characteristics of ALK-negative ALCL with primary bone involvement is presented. ALCL should be considered in patients not responding to therapies for osteomyelitis.

BACKGROUND

Anaplastic large cell lymphoma (ALCL) is a subtype of a relatively rare group of peripheral T-cell lymphomas. There are two types of systemic ALCL: ALK-positive ALCL and ALK-negative ALCL. The ALK-negative form usually has a less favourable prognosis compared to the ALK-positive form, although good prognosis has been described among ALK-negative subsets with particular genetic rearrangements.¹ The estimated 5-year overall survival in adults with systemic ALK-negative ALCL is ~30–49% compared to 70–86% in ALK-positive ALCL.² Therefore, early diagnosis of ALCL is crucial for prompt treatment. Systemic ALCL frequently presents with nodal involvement, but in rare cases, the disease presents with primary bone lesions. This unusual presentation can lead to misdiagnosis and delay in the initiation of treatment. There have been case reports of ALK-positive ALCL presenting in the bone in the paediatric and adult population, but ALK-negative ALCL with bone involvement is extremely rare.^{3 4} In this report, we describe a 50-year-old man who presented with pain and swelling over his left anterior shoulder 6 months after left rotator cuff repair and was ultimately diagnosed with ALK-negative ALCL.

CASE PRESENTATION

A 50-year-old Caucasian man presented to the Veterans Affairs Medical Center in Washington, DC, with swelling, erythema and recurrent pain at the site of a rotator cuff repair performed 6 months previously. His symptoms were not relieved by methylprednisolone and oxycodone/acetaminophen. On follow-up, he reported several days of subjective fevers, chills and nausea. His surgical history was notable for a left shoulder rotator cuff repair at an outside hospital 3 years earlier. Notably, he had no other systemic symptoms, including weight loss or night sweats.

Physical examination revealed the patient to be afebrile. The left shoulder was edematous and painful over the subacromial bursa with decreased range of motion of the shoulder joint. Purulent fluid was aspirated and sent for gram stain and cultures before he was started on antibiotics. He was admitted for debridement for presumed septic arthritis.

INVESTIGATIONS

A contrast-enhanced MRI of his left shoulder revealed a large rim-enhancing fluid collection within the subacromial subdeltoid bursa and a rim-enhancing fluid collection within the subcoracoid bursa (figure 1). There was abnormal signal enhancement of the humeral head, acromion and distal clavicle consistent with osteomyelitis.

At the time, inflammatory markers showed an erythrocyte sedimentation rate (ESR) of 97 mm/hour and a C reactive protein (CRP) of 19.7 mg/dL. His white cell count (WCC) was 11 600 with 71% neutrophils. The shoulder bursa aspiration revealed 190 000 WCCs and 43 000 red blood cells. The gram stain from the aspiration showed no organisms, and the cultures were no growth; similarly, blood cultures were no growth.

Intraoperatively, the orthopaedists encountered purulent fluid, which was lavaged. Affected areas of bone and necrotic tissue were debrided.

Figure 1 T2-weighted contrast image of the patient's left shoulder, demonstrating a large loculated abscess (star) within the subacromial deltoid bursa along with presumed osteomyelitis of the humeral head (arrow).

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DIFFERENTIAL DIAGNOSIS

In consultation with infectious diseases, tissue and bone were also sent for smear and culture for acid-fast bacilli (AFB) and routine cultures were held for 1 week in an attempt to grow *propionibacterium acnes* and other fastidious bacteria. No microorganisms were isolated from the intraoperative cultures. The patient was kept on vancomycin and piperacillin/tazobactam as an inpatient and discharged on 3 months of amoxicillin/clavulanate and rifampin for empiric treatment of osteomyelitis and septic arthritis.

At the time, primary bone tumours such as osteosarcoma, chondrosarcoma and lymphoma were felt to be much less likely given the clinical presentation and the results of diagnostic testing.

TREATMENT

One week after the debridement, the patient presented with copious amounts of purulent drainage from the incision site. He underwent repeat debridement and removal of anchor sutures. Antibiotics were held the day prior to surgery. Aerobic, anaerobic and fungal cultures obtained intraoperatively were again no growth. He was treated for osteomyelitis and septic arthritis empirically with ertapenem and vancomycin for six additional weeks.

Throughout the months that followed, the patient continued to have persistent purulent drainage. Repeat MRI demonstrated findings concerning for progression of osteomyelitis. He underwent two more debridements.

OUTCOME AND FOLLOW-UP

Ten months after his initial surgery, he was noted to have enlarging, firm and tender left supraclavicular and axillary lymph nodes, night sweats and temperatures up to 38°C. Incisional biopsy of the supraclavicular lymph node showed numerous anaplastic large cells. The tumour cells were strongly positive for CD30, epithelial membrane antigen and negative for ALK1. The findings were conclusive for ALK-negative ALCL. As a result of these findings, surgical pathology from the initial surgery was re-examined. Atypical cells had originally been identified, but interpreted as benign because immunostains were negative for markers including AE1/AE3, CD45, CD3, CD20, CD1A and S100. Re-examination of the supraclavicular lymph node using the additional immunostain for CD30 demonstrated involvement of ALCL from the initial biopsy (figure 2).

In the days prior to chemotherapy, he began to notice new cutaneous lesions. PET/CT scan revealed disease involving his left humeral head, soft tissue, skin and supraclavicular and axillary lymph nodes. After initiation of etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin (EPOCH), the cutaneous shoulder lesions quickly improved and he required no further antibiotic or surgical therapy (figure 3). After three cycles, the patient experienced dramatic clinical improvement; he no longer experiences pain, and while range of motion is still limited, it is improved. He completed six cycles of chemotherapy and now, approaching 2 years from diagnosis, he has no evidence of disease.

DISCUSSION

Primary bone lymphomas (PBL) are extremely rare, making up ~2% of all non-Hodgkin's lymphoma (NHL).⁵ While most PBLs are large B-cell lymphomas, ALK-positive ALCL is the second most common pathology encountered. ALK-negative ALCL remains an extremely rare form of PBL.^{6 7} Systemic ALK-negative ALCL is distinguished from ALK-positive ALCL

Figure 2 Immunohistochemistry from a supraclavicular lymph node demonstrating strong membrane and Golgi staining for CD30 and negative staining for CD45, CD3 and CD20.

Figure 3 Positron emission tomography/CT before and 4 months after starting chemotherapy. (1) Intensely fluorine-labeled deoxyglucose (FDG) avid axillary adenopathy, subcutaneous tissues and left humeral head; (2) complete resolution of FDG uptake in the left axillary fossa lymphadenopathy and significantly decreased FDG uptake in the left shoulder after six cycles of chemotherapy.

in that it presents in older patients and usually has a less favourable prognosis. The unique characteristics of ALK-negative ALCL with primary bone involvement are not fully understood.⁷

As in our case, PBL is often misdiagnosed, which delays treatment. In our review of cases of patients with ALK-negative ALCL with primary bone involvement, three of seven were initially diagnosed as osteomyelitis with signs and symptoms including bone pain, fever, elevated inflammatory markers and osteolytic lesions (table 1). Note the articles informing the information presented in table 1 are from articles available in English. There was one article on the clinicopathologic features and prognosis of primary bone ALCL that was only available in Chinese and, therefore, is not included.⁸ However, only two other patients had disease localised to a single site at the time of presentation.

Like systemic ALCL, primary bone ALCL has an increased prevalence in men.⁴ The majority of the cases in our review were men (five of seven). Systemic ALK-negative ALCL is also known to occur in an older patient population (ages 55–60) as compared with systemic ALK-positive ALCL (ages 25–35).² The majority of the cases in our review were age 50 and older (four of seven). In terms of prognosis, systemic ALCL is known to be

Table 1 Characteristics of patients with ALK-negative ALCL presenting in bone

Study	Age; gender	Race	Presenting symptoms; impression	Locations	Localised vs multisite disease	Labs	Therapy	Prognosis
Nagasaka <i>et al</i> ⁴	24 F	Japanese	Fever and right buttock pain; osteomyelitis vs giant cell tumour	Left ilium	Localised	Elevated ESR and leucocytosis	CHOP×1 cycle	Died of disease, 1 year after initial presentation
Nagasaka <i>et al</i> ⁴	30 M	Japanese	Tenderness of right 6th costal bone; osteomyelitis	Right ilium, right rib	Multisite	Unremarkable	CHOP×1 cycle and autologous peripheral blood stem cell transplantation	Alive with disease, 2 years after initial presentation
Nagasaka <i>et al</i> ⁴	50 M	Japanese	Back pain and fever; metastatic malignancy of unknown origin	Vertebra bones (T6, L2, L3, S1)	Multisite	Elevated LDH and CRP	CHOP×1 cycle and irradiation	Alive with disease, 2 years later
Jones <i>et al</i> ⁹	45 M	Unknown	Unknown; tumour	Humerus and abdominal node	Multisite	Unknown	CHOP×2 cycles and irradiation	Local extension, died of disease, 10 months
Jones <i>et al</i> ⁹	55 M	Unknown	Unknown; carcinoma	Alveolar ridge and palate	Multisite	Unknown	CHOP×6 cycles	No evidence of disease, 12 months
Leung and Kwong ⁷	57 F	Unknown	Fever and bone pain; unknown	Vertebral column, limb girdles, proximal long bones	Multisite	Unremarkable (WCC 3.2 ×10 ⁹ /L)	Unknown	Unknown
Mika <i>et al</i> ⁶	60 M	Unknown	Pain, B-symptoms; osteomyelitis	Right Os sacrum	Localised	Elevated inflammatory markers	Unknown	Unknown

ALK, anaplastic lymphoma kinase; ALCL, anaplastic large cell lymphoma; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; F, female; LDH, lactate dehydrogenase; M, male; S, sacral; T, thoracic; L, lumbar; WCC, white cell count.

an aggressive lymphoma, with ALK-1 expression being a poor prognostic marker.⁷ The prognosis of ALCL with primary bone involvement appears to be poor as well. According to Nagasaka, five of six cases of ALCL with bone involvement had unfavourable prognoses.⁴ Interestingly, this was regardless of ALK-1 expression, putting into question if ALK-1 expression serves as a poor prognostic marker in bone the same way it does in nodal ALCL. Although the prognostic value of ALK-1 in bone is not clear, timely diagnosis is crucial for early initiation of treatment, as primary bone ALCL appears to have an overall poor prognosis.

Treatment of ALCL for individuals <60 years old, such as our patient, typically includes EPOCH times six to eight cycles with consideration for autologous haematopoietic cell transplantation depending on response to therapy and the risk of relapse. Radiation therapy is also a consideration for those who do not have a complete response or are intolerant to chemotherapy.¹⁰

While our patient shared similarities with other cases, he displayed unique features such as concomitant soft tissue involvement with later spread to lymph nodes. He also had the unique history of two prior rotator cuff surgeries and biceps tendonecrosis with placement of anchor sutures. The first surgery was 3 years prior to presentation and the second 6 months prior to presentation.

Though rarely seen, lymphomas have been known to develop around prosthetic devices and other types of implants. Such cases have been described as presenting with pain, erythema and swelling at the surgical site, sometimes years after surgery.^{11–14} Although our patient did not have a prosthesis or implant, the anchor sutures may carry similar risk as they may be made of foreign material such as metal or plastic. Whether this patient's ALCL was directly related to his prior surgery and anchor sutures is unknown. The mechanism is not fully understood.^{11–14}

Patient's perspective

The patient was offered the opportunity to provide his perspective of his experience on multiple occasions, but he declined.

Learning points

- ▶ Anaplastic large cell lymphoma (ALCL) presenting in bone is rare and often leads to delayed diagnosis.
- ▶ ALK-negative ALCL tends to occur in older individuals and often portends a poor prognosis.
- ▶ There may be an association with the development of ALCL with foreign material at prior surgical sites.
- ▶ There should be a consideration for primary bone lymphoma in individuals not responding to therapy for osteomyelitis.

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