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CASE REPORT

Varatharaj Mounasamy
Stephen Berns
E. Michel Azouz
Vincent Giusti
D. Raymond Knapp

Anaplastic large cell lymphoma presenting as an epiphyseal lytic lesion—a case report with clinico-pathologic correlation

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Study conducted at the Nemour's Children's Clinic and Orlando Regional medical center, Orlando, Florida.

V. Mounasamy (✉)
1289 Swan Lake Drive Apt 306,
Charlottesville, VA 22902, USA
e-mail: Vartharajm@hotmail.com
Tel.: +1-786-266-5072

V. Mounasamy
Nemours Children's Clinic,
Orlando, FL, USA

S. Berns
Department of Pathology,
Orlando Regional Medical Center,
Orlando, FL, USA

E. M. Azouz
Department of Diagnostic Imaging,
Children's Hospital of Eastern Ontario,
Ottawa, Canada

V. Giusti
Hematology Division,
Nemours Children's Clinic,
Orlando, FL, USA

D. R. Knapp
Nemours Children's Clinic,
Orlando, FL, USA

Abstract Anaplastic large cell lymphoma (ALCL) is predominantly a systemic disease with nodal involvement, but extranodal involvement can occur either as the primary presentation or during the disease course. Primary epiphyseal involvement is extremely rare with lymphomas. This case report illustrates an 8-year old boy who first presented with pain over the right upper extremity, which was initially treated as epiphyseal osteomyelitis. A few weeks later, he presented with abdominal pain and an abdominal wall mass, which on biopsy proved to be an anaplastic large-cell lymphoma.

Case report

An 8-year-old Caucasian boy presented with a complaint of right upper extremity pain and restricted movements of the right shoulder for the past 3 months. His pediatrician initially evaluated him, when pain was localized to the elbow. Radiographs and MR imaging of the right elbow were normal. He was referred to physical therapy for mobilization and treatment. He had persistent right upper extremity pain and was evaluated by a chiropractor. In view of persistent discomfort, the patient was referred to our institution for re-evaluation and treatment.

At presentation to our clinic, he described intermittent right upper extremity pain, which had progressively increased in severity over the past 3 months and had become persistent. He described the pain as dull-achy in nature, worse at night and present both at rest and with activity. He had difficulty in actively using his right upper extremity. The patient denied any significant history of trauma or injury to the affected shoulder and elbow, but had had a trivial fall a month back. His past medical and surgical history were unremarkable, and he denied any constitutional symptoms such as fever, chills, or weight loss.

Physical examination revealed an 8-year-old healthy male. Examination of his right upper extremity revealed atrophy of muscles around the right shoulder. The right shoulder was not tender, and no mass was palpable. The patient was able to initiate abduction, but was not able to maintain active abduction and had weakness of the muscles around the right shoulder with grade III power. He had full passive range of motion at the right shoulder. There was no

axillary adenopathy. He had good active range of movements in the elbow, wrist and hand. Examination of the neck, left upper extremity and both lower extremities revealed no abnormality.

Radiographs of the right shoulder appeared normal. MR imaging of the cervical and thoracic spine were normal. MR imaging of the right shoulder showed an abnormal signal involving the lateral two thirds of the proximal humeral epiphysis. This lesion had a T1-weighted hypointensity (Fig. 1) and T2-weighted hyperintensity (Fig. 2), with post-gadolinium enhancement. No soft-tissue swelling, mass or abnormal enhancement was noted. The rest of the humerus was normal.

He had an erythrocyte sedimentation rate (ESR) of 67 mm/hr and a normal white blood cell count.

After consultation with a musculoskeletal oncologist, the patient was empirically started on intravenous antibiotics, with an assumed diagnosis of osteomyelitis of the right proximal humeral epiphysis. There was a response to the antibiotic therapy, and the ESR dropped to 6 mm/hr.

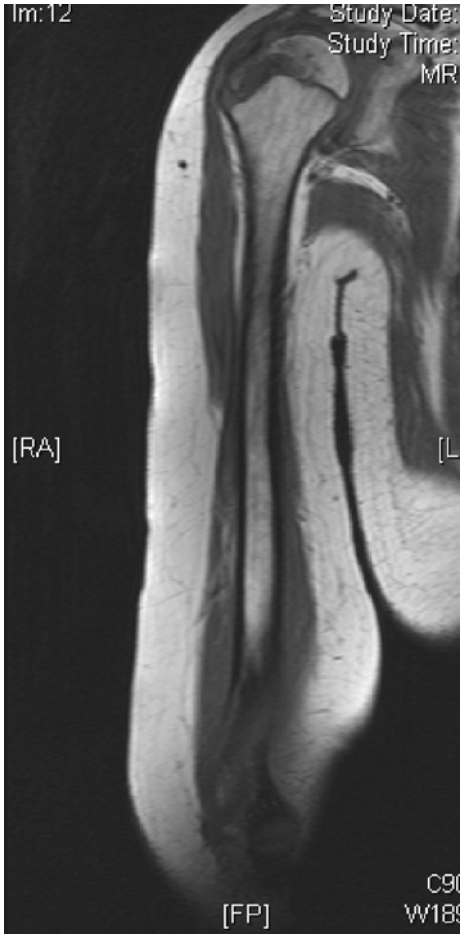

Fig. 1 T1-weighted coronal MR image showing hypointense signal in the lateral two thirds of the right proximal humeral epiphysis. No soft-tissue mass is seen. The rest of the humerus is normal

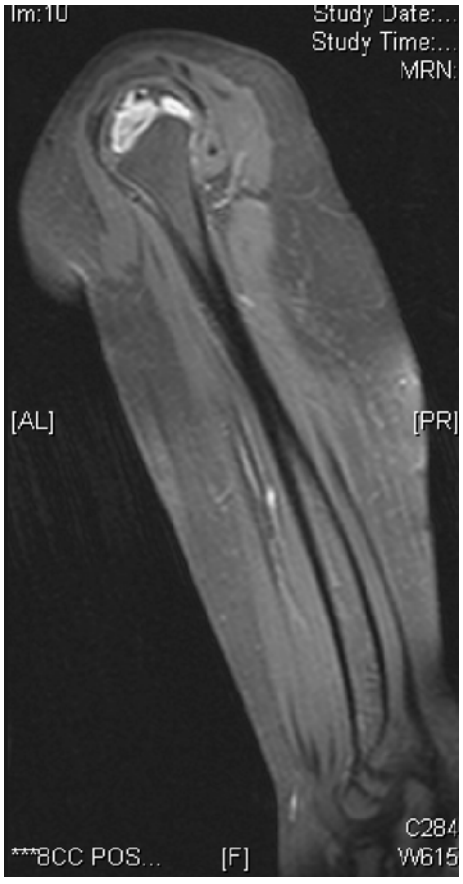

Fig. 2 T2-weighted sagittal MR image, with fat suppression, showing hyperintense signal in that same epiphyseal lesion

Repeat radiographs of the right shoulder revealed a lytic lesion in the humeral head (Fig. 3). This was confirmed and better delineated using axial computed tomography (CT) scanning, which showed a well-defined purely lytic lesion in the anterior and lateral aspects of the proximal humeral epiphysis, with no matrix calcification (Fig. 4).

Eight weeks later, he presented with left lower abdominal pain. Clinical examination, ultrasound and CT studies of the abdomen and pelvis revealed a mass arising from the left lower abdominal wall, extending into the pelvis and indenting the urinary bladder (Fig. 5). A positron emission tomography scan showed increased metabolic activity over the right proximal humerus and the left anterior abdominal wall (Fig. 6). Radiographs now showed enlargement of the lytic lesion of the proximal humeral epiphysis.

Open biopsy of the lower abdominal mass was performed, and the histopathologic diagnosis was anaplastic large-cell lymphoma (ALCL). A CT-guided biopsy of the right proximal humeral epiphysis lesion confirmed the diagnosis of ALCL. Bone-marrow studies showed a trilineage hyperplasia with normal myeloid/erythroid ratio. The touch prep and histology demonstrated sheets of non-cohesive large, anaplastic cells. Many hallmark cells were present which had horseshoe-shaped nuclei and

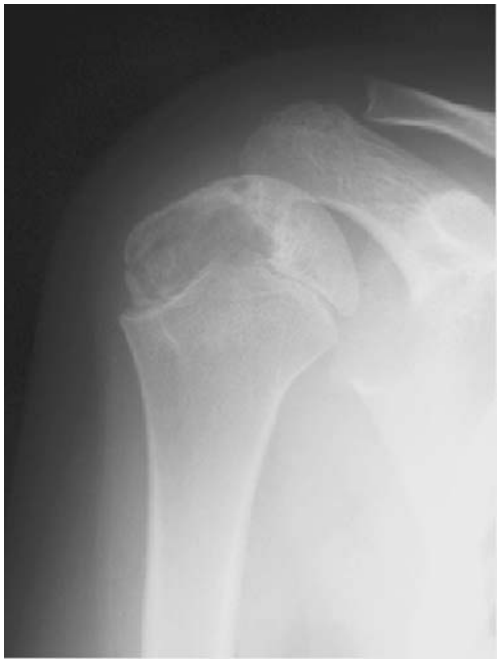

Fig. 3 AP radiograph of the right shoulder now reveals a lytic lesion in the lateral two thirds of the proximal humeral epiphysis. There is no marginal sclerosis. No other sclerotic or lytic bone lesion is seen. The shoulder and the acromioclavicular joints are normal

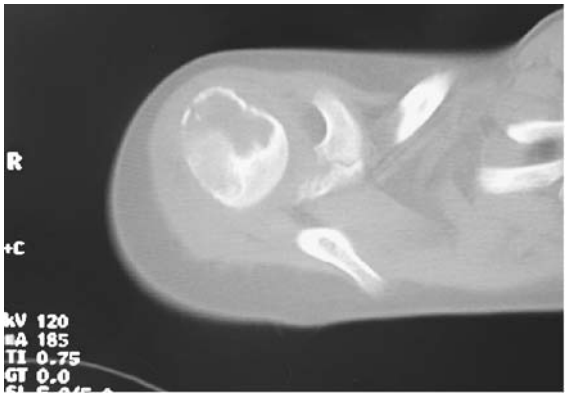

Fig. 4 Axial CT image of the right shoulder better delineates the well-defined purely lytic lesion in the anterior and lateral aspects of the proximal humeral epiphysis, with no matrix calcification, marginal sclerosis, periosteal reaction or soft-tissue mass

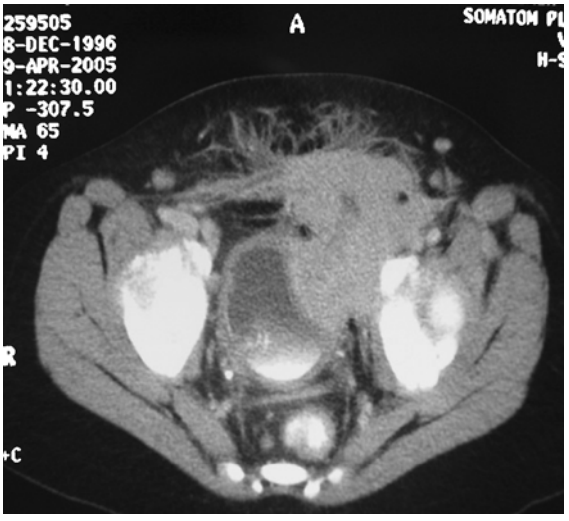

Fig. 5 Axial CT image of the pelvis reveals a mass arising from the left lower abdominal wall extending into the pelvis and indenting the urinary bladder

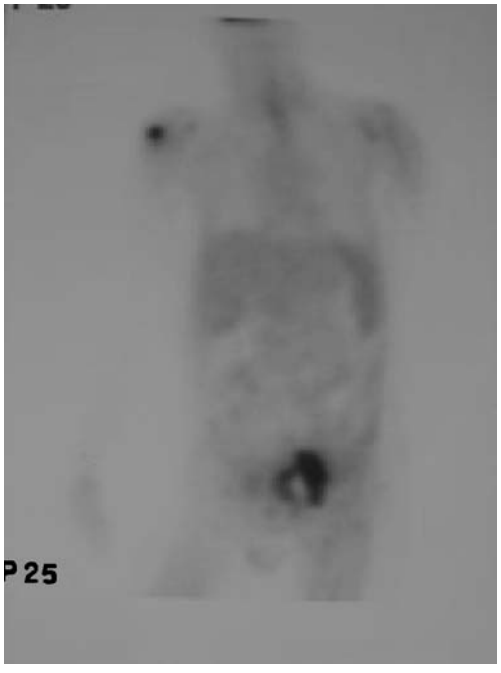

Fig. 6 PET scan showing an area of increased activity over the right proximal humerus and over the left side of the pelvis

dense eosinophilic cytoplasm. Other smaller forms and giant cell forms were present (Fig. 7).

Multiple immunohistochemical stains were performed, including ALK-1, CD30, CD20, CD79a, and CD45. The T-cell markers CD3, CD4, CD5, and CD8 were also performed. The tumor had strong immunohistochemical staining expression of ALK-1 (Fig. 8), moderate immunohistochemical expression of CD30 (Fig. 9), and focal immunohistochemical positivity for CD4. This is demonstrated by the the amount of deposition of brown pigment from a peroxidase enzyme reaction which is attached to a monoclonal antibody to these proteins. This confirmed the initial morphologic diagnosis of ALCL.

Fluorescent in-situ hybridization studies found a rearrangement of the ALK gene region at 2p23 in 91% of the interphase nuclei. Cytogenetic studies found an abnormal near-tetraploid clone with t (2;5)(p23;q35). Other abnormalities, including additional material on 8q and 21q, were present. Derivative 16 and 17 chromosomes with translocation of 1q and loss of 10, 15, and 22 were found. A subclone with additional material of unknown origin on 6q

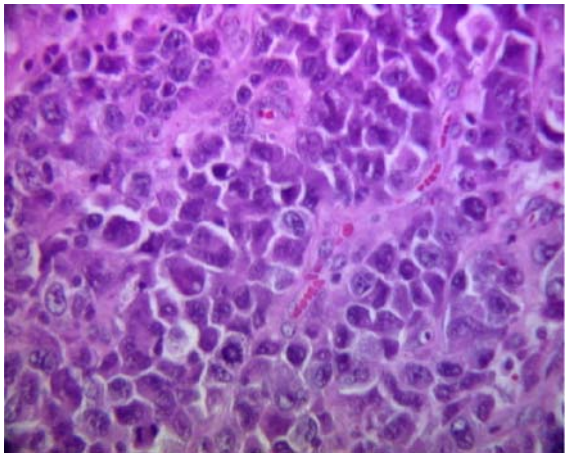

Fig. 7 Histopathologic section, 600× H & E, demonstrates sheets of non-cohesive large anaplastic cells with many hallmark cells present. These have horseshoe-shaped nuclei and dense eosinophilic cytoplasm. Other smaller forms and giant cell forms were present

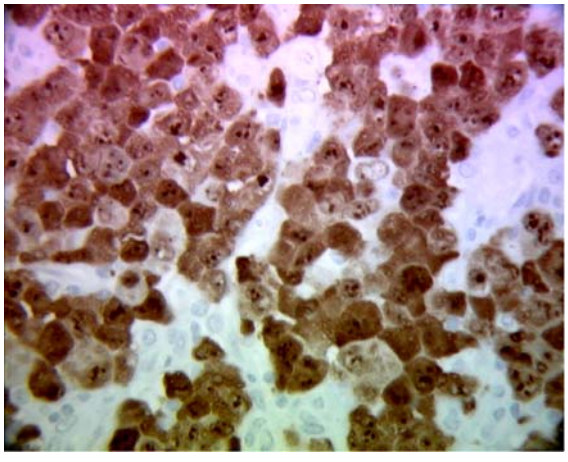

Fig. 8 Section of tumor cells strongly expressing ALK-1

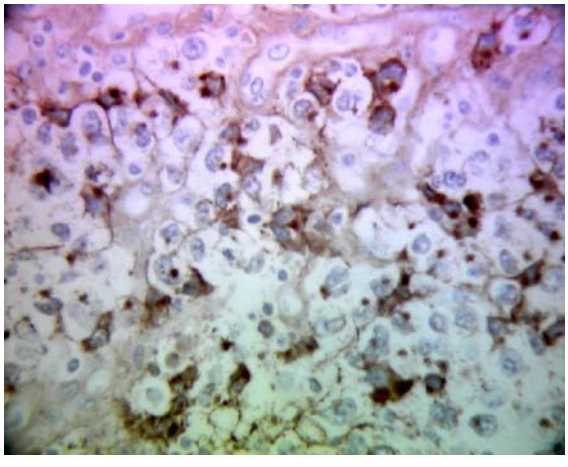

Fig. 9 Section of tumor cells showing moderate expression of CD30 immunoreactivity

and gain of a marker chromosome was also found. These molecular studies confirmed the previous diagnosis of anaplastic large-cell lymphoma.

Skin punch biopsy did not reveal any abnormal lymphoid infiltrates and a CT scan of the brain, and cerebrospinal fluid analysis were normal.

The patient is presently receiving chemotherapy.

On a recent visit, he had improved shoulder function, but radiographs revealed persistence of the lytic lesion in the right proximal humeral epiphysis. A recent PET scan (after chemotherapy) revealed interval resolution of the increased metabolic activity, in both the proximal humerus and the lower left abdomen and pelvis.

Discussion

Non-Hodgkin's lymphoma involving bone is uncommon, and epiphyseal involvement is extremely rare, especially at presentation. CD30 positive anaplastic large-cell lymphoma is a type of non-Hodgkin's lymphoma associated with a specific chromosome translocation between chromosomes 2 and 5. ALCL is a neoplasm of T-cell or null cell lineage, and represents 2% of all non-Hodgkin's lymphomas. ALCL belongs to a new category of lymphomas, and is defined on the basis of the anaplastic appearance of its tumor cells, their propensity to grow cohesively and to invade lymph-node sinuses, and consistent expression of cytokine receptor CD30 on all or nearly all neoplastic cells [1].

ALCL, which is also known as Ki-1 lymphoma, occurs more often in young male patients, in the first three decades of life, and has a better prognosis than histologically similar B-cell neoplasms. It is frequently associated with systemic symptoms and extra-nodal involvement, especially skin, but both single bone involvement, and epiphyseal localization at presentation are extremely rare. Bone-marrow and CNS involvement are uncommon, whilst lymphadenopathy is seen in 90% of the cases. Clinically, ALCL is subdivided as primary (systemic and cutaneous) and secondary, which is anaplastic transformation of other lymphomas, occurring in older patients. Immunocytochemical distinction of ALK-positive versus the ALK-negative ALCL seen in older patients is clinically important, since the latter has a very bad prognosis [2]. ALCL primarily involves nodal as well as extra-nodal (skin) sites, but primary or secondary bone involvement is rare [3].

The spine, pelvis, ribs and femora are frequent sites of bone involvement in non-Hodgkin's lymphoma. Most of the lesions are osteolytic, but these may vary widely from a well-defined geographic to a moth-eaten or permeative pattern. Bone lesions are often accompanied by a soft-tissue mass. A geographic lesion may show marginal sclerosis. Pathologic fractures may complicate large lesions, and may be the presenting feature. Expansile bone lesions as well as periosteal reaction are uncommon.

Sclerotic bone lesions are rare, and are associated with smudged destruction of the bony trabeculae [4].

Except for clear cell chondrosarcoma, it is extremely unusual for malignancy to present as an epiphyseal lytic lesion in the pediatric age group. Primary epiphyseal malignant involvement may be seen with clear cell chondrosarcoma, osteosarcoma [5], Ewing's tumor and lymphoma [6, 7].

Chondroblastoma is a benign cartilaginous lesion, well-known to involve the epiphysis, almost exclusively. It is the classical epiphyseal neoplasm. The lesion is well-defined, round, oval or lobulated, often with a surrounding sclerotic rim. Cartilaginous matrix calcification is frequently seen on radiographs or CT, and the lesion usually shows no aggressive feature.

In a study of 15 solitary lucent epiphyseal lesions in children, previously published by one of us (EMA), it was found that eight were due to bone infection/inflammation, four were benign cartilaginous lesions, two were osteoid osteomas with an epiphyseal nidus, and one was an eosinophilic granuloma [8]. When we include mycobacterial infections and foreign-body granulomas, osteomyelitis accounts for more than 50% of the pure epiphyseal lytic lesions. Acute, subacute and chronic bone infection may be localized primarily in the epiphysis. Diagnosis may be difficult and delayed [9, 10]. The epiphyseal abscess is usually well-defined, with a sclerotic rim and purely lytic. Adjacent primary or secondary joint infection is common. In our opinion, the presence or absence of a sclerotic rim in an epiphyseal lytic lesion does not seem to narrow the differential diagnosis. Biopsy and/or excision are needed for final histopathologic diagnosis.

Other benign lesions which may be primarily epiphyseal include giant cell tumor, hemangioma/lymphangioma, intraosseous lipoma, benign fibrous histiocytoma and intraosseous ganglion [11]. Both giant cell tumor of bone and intraosseous lipoma are rarely seen in children.

Malignancy confined to the epiphysis of a long bone in a child as the cause of presentation is an exceptional occurrence.

Conclusion

In this report we describe a case of ALK-1 positive ALCL, of the null cell type, that presented as an epiphyseal lytic lesion in the proximal humerus of an 8-year-old boy. ALK-1 positive ALCL, of the null cell type with bone involvement has been reported, but we are not aware of a case involving primarily the epiphysis.

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