CASE REPORT

Anaplastic large T-cell lymphoma presenting as an isolated osseous involvement: a case report and review of the literature

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SUMMARY

This case describes a 50-year-old man with multiple lytic bone lesions involving the skull, pelvis and ribs and associated features of anaemia, hypercalcaemia, azotaemia and subsequently found to be non-Hodgkin's lymphoma of anaplastic large T cell type (ALCL) on biopsy taken from a soft tissue mass in the anterior chest wall as an aetiology. We report this case with an aim to expand our knowledge of isolated osseous involvement in case of non-Hodgkin's lymphoma. This case was unique in the sense of an isolated osseous involvement in ALCL without any organomegaly and lymphadenopathy with a normal bone marrow biopsy finding. So in rare instances, T-cell lymphoma can present with a multiple lytic lesion, anaemia, hypercalcaemia. Although B-cell non-Hodgkin's lymphoma can present with the above manifestation, it is extremely rare for T-cell non-Hodgkin's lymphoma.

BACKGROUND

Anaplastic large T-cell lymphoma (ALCL), also called Ki-1 lymphoma, is a morphologically and immunologically distinct subset of non-Hodgkin's lymphoma (NHL) characterised by the proliferation of pleomorphic large neoplastic lymphoid cells, which strongly express the CD30 antigen (Ki-1 antigen), usually growing in a cohesive pattern and preferentially spreading in the lymph node sinuses.^{1 2}

Two distinct clinical forms of primary ALCL are now recognised: limited to the skin and systemic. Systemic ALCL has an aggressive clinical course and patients frequently present with systemic symptoms, advanced-stage disease and extranodal localisations.^{3 4} Response to treatment and overall survival of systemic ALCL in children are good. In adults, however, it is not clear.

Anaplastic and angioimmunoblastic lymphomas show diffuse systemic involvement but presentation with only multiple lytic lesions (isolated osseous involvement) is rare. Our patient happened to be one of those rare cases.

CASE PRESENTATION

A 50-year-old North Indian man was admitted with symptoms of intermittent chest pain, generalised weakness and significant weight loss over the past 3 months. He described his intermittent chest pain as dull, aching, increasing in severity over the past 1 month, worsening at night and present both at rest and with activity. He had difficulty in actively

using both his lower limbs. The patient denied any significant history of trauma or fall. His medical and surgical history was unremarkable and he denied any constitutional symptoms of fever, chills, cough, dyspnoea or altered bowel habits. Physical examination showed no abnormalities except for pallor and tenderness on palpation of the patient's upper arms, anterior thorax and lower spine. There were no significant palpable peripheral lymph nodes or any cutaneous lesions. Systemic examinations were essentially normal.

INVESTIGATIONS

The results of laboratory studies were as follows: haemoglobin 7 g/dl (normal 11–15 g/dl) with normal platelet and white cell count. Peripheral smear revealed normochromic normocytic anaemia with a reticulocyte count of 2.1% (normal 0.2–2%). Other investigation revealed blood urea nitrogen 76 mg/dl (normal up to 40 mg%), serum creatine 2.3 mg/dl (normal 0.6–1.2 mg%), calcium 11.8 mg/dl (normal range 9–10.5 mg%), serum phosphate 3.8 mg/dl (normal range 3–4.5 mg%), serum lactate dehydrogenase -804 (normal up to 200), serum alkaline phosphatase 154 units, total serum proteins 7.4 g% (alb 3.8 g%), A/G ratio of 1.1, serum uric acid 8.4 mg%, with a normal urinary and lipid profile report. Serum prostate specific antigen and parathyroid hormone (PTH) were normal. The erythrocyte sedimentation rate was 139 (normal up to 30) in the first hour.

A skeletal survey revealed multiple osteolytic lesions in the ribs, pelvis and skull bones with no reactive bone formation (figures 1 and 2). ECG was normal. Ultrasonography was normal. MRI of the

Figure 1 Skiagram of the skull bone showing multiple lytic lesions.

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Figure 2 Skiagram of the pelvis bone showing multiple lytic lesions.

abdomen revealed an essentially normal study with the exception of a bulky bilateral kidney. Kidney biopsy was normal. Serum electrophoresis revealed an M band composed of α -globulin and urine negative for Bence Jones proteins. The bone marrow aspirate and biopsy specimen were normal (<3% plasma cells). The results of serum and urinary protein electrophoresis and the serum 1,25-dihydroxyvitamin D level were also normal. In the meantime, he received conservative management; his renal parameters normalised on fluid and diuretics therapy, and his anaemia was corrected.

On contract CT scan of studies of the neck, thorax, abdomen and pelvis showed no abnormalities except for the previously described multiple osteolytic lesions in the ribs along with a soft tissue mass of 1.5×1.5 cm in the anterior chest wall adjacent to the fourth and fifth right ribs.

A biopsy from the anterior chest wall mass revealed fibrous tissue infiltrated with sheets of non-cohesive large anaplastic cells with many hallmark cells which have a scanty cytoplasm and hyperchromatic nuclei (figures 3 and 4). There was a variation in the nuclear size; the tumour cells showed immunoreactivity for leucocyte common antigen (LCA), focal immunoreactivity for LCA and focal immunoreactivity for CD45RO (T-cell marker) and CD30 (figures 5, 6 and 7). There was no immunoreactivity for CD 20 (B-cell marker), κ or λ light chain or cytokeratin. The histological findings were consistent with NHL of ALCL. Sampling from lytic lesions also

Figure 3 Biopsy from the anterior chest wall mass revealed fibrous tissue infiltrated by a tumour composed of cells which have a scanty cytoplasm and hyperchromatic nuclei (H&E ×40). There was a variation in the nuclear size.

Figure 4 Biopsy from the anterior chest wall mass revealed fibrous tissue infiltrated by a tumour composed of cells which have a scanty cytoplasm and hyperchromatic nuclei (H&E ×40). There was a variation in the nuclear size.

revealed similar findings. The results of repeated serum and urinary protein electrophoresis were normal. Repeated bone marrow aspiration and biopsy revealed no abnormal cells, infiltrates or fibrosis.

DIFFERENTIAL DIAGNOSIS

- Multiple myeloma
- NHL

TREATMENT

The patient had already received three cycles of cyclophosphamide, doxorubicin, vincristine and prednisone, and we planned to repeat a biopsy and a radiological examination after completion of the fourth cycle of therapy.

OUTCOME AND FOLLOW-UP

The patient unfortunately succumbed to infectious complications in another hospital at his native place.

DISCUSSION

ALCL is a rare disease, accounting for <5% of all cases of non-NHL.¹ ALCL was first described as a clinical entity in 1985 based upon its unique characteristic of cohesive proliferation of large pleomorphic cells expressing CD 30 (Ki-1).³ ALCL has a

Figure 5 The tumour cells showed immunoreactivity for leucocyte common antigen ×40.

Figure 6 The tumour cells showed immunoreactivity for CD45RO (T cell marker), $\times 40$.

peak incidence in childhood and accounts for approximately 40% of NHL cases diagnosed in paediatric populations.⁵

Patients with ALCL were significantly younger than those with non-ALCL. B symptoms were more frequent in ALCL. A majority of patients with ALCL had a disseminated disease (Ann Arbor stage III or IV) and a limited number of extranodal sites.⁶ Bone marrow involvement has been initially considered as a rare event in ALCL.⁷ When immunohistochemistry with anti-CD30 and anti-EMA are used to study bone marrow samples, malignant cells are often detected in as much as 43% of the cases.⁸ In our case, even a repeated bone marrow biopsy did not reveal any bone marrow involvement.

There are no clear risk factors for developing ALCL. Some reports have suggested that Epstein-Barr virus (EBV) is important in the pathogenesis of ALCL. However, a recent series of 64 ALCL cases revealed no EBV-encoded RNA or immunohistochemistry evidence for EBV-latent membrane protein type 1.⁹ EBV may be aetiologically associated with ALCL, but in our case we have not tested for EBV infection.

ALCL occurs as two distinct clinical entities, a cutaneous and a systemic variant; systemic ALCL is generally very aggressive. The majority of patients present with stage III or IV disease and have systemic symptoms.¹⁰ Extranodal disease occurs in 40–60% of patients, with skin, bone, soft tissue and lung being common sites of involvement.¹¹ This patient bears a unique presentation of diffuse lytic bony involvement with soft tissue swelling adjacent to the third and fourth ribs without any skin involvement.

In an adult with widespread lytic bone lesions, hypercalcaemia and deranged renal function that is not mediated by PTH,

Figure 7 The tumour cells showed immunoreactivity for CD30, $\times 40$.

diagnostic testing for myeloma and metastatic cancer is the obvious strategy. But in this patient, this strategy seemed to fail, since all the tests, including normal bone marrow findings, normal results of protein electrophoresis and normal internal organ imaging, make the diagnosis of the above entity unlikely.

Mycobacterium, fungal and chronic salmonella infections can cause lytic bone lesions with lung involvement. However, the extensive nature of the bone lesions, the absence of prior fever and the temporal course of the illness make these highly unlikely explanations for the patient's entire illness.

Diagnosis is established by typical morphology and immunohistochemistry. ALCL consists of large blastic cells with round or pleomorphic nuclei. About 60% of ALCLs express one or more T cell-associated antigens, such as CD3, CD43 or CD45RO, in which cytotoxic granule proteins are often present.¹² In the presence of typical morphology, immunohistochemical detection of CD30 expression is particularly useful for the diagnosis of the lymphohistiocytic variant, which was observed in our patient.⁷

Although no large comparative studies have been published, most investigators reported that the response of ALCL to chemotherapy was good, ranging from 60% to 90%. The overall survival of localised disease is known to be good, especially in children. More advanced stages have a high relapse rate and their prognosis in comparison to that of other large-cell lymphomas is controversial.^{13–15}

There were only two case series regarding osseous involvement in the ALCLs published to date. Nagasaka *et al* described six unusual cases of ALCL primarily presented as osteolytic bone lesions, with a predilection for the axial bones. Most (4/6) tumours were of null-cell lineage; all the cases tested were positive for granzyme B, and five of six have had relatively poor clinical outcome. Other findings also suggest that, unlike nodal ALCL, ALK-1 positivity is not a favourable prognostic feature for patients with primary bone ALCL. These findings further support the concept that the clinical behaviour and pathogenesis of ALCL may vary according to the involved anatomic sites.¹⁶

So in conclusion, ALCL is a rare but biologically well-characterised disorder with a wide spectrum of presentation. It may present with isolated osseous involvement. Recognition of a combination of symptoms including anaemia, renal failure and bone pain in the presence of normal bone marrow biopsy and serum electrophoresis should trigger aggressive clinical work up to rule out the possibility of lymphoma. A meticulous examination of early biopsies based on CT and MRI of deeply situated soft tissue or lymphnodes are recommended to yield an early diagnosis of ALCL.

Learning points

- ▶ Anaplastic T-cell lymphoma (ALCL) is a rare but biologically well-characterised disorder with a wide spectrum of presentation but may present with isolated osseous involvement.
- ▶ Any old age patient with anaemia, renal failure and bone pain in the presence of normal bone marrow biopsy and serum electrophoresis should trigger aggressive clinical workup to rule out the possibility of lymphoma.
- ▶ A meticulous examination in the form of early biopsies based on CT and MRI of deeply situated soft tissue or lymphnodes is recommended to yield an early diagnosis of ALCL.

Contributors HKN was involved in conceptualisation of the manuscript, search of literature and drafting and writing the manuscript, head of the resident team managing the patient. MKD vital inputs in drafting and editing of the manuscript, supervised clinical management of the patient being the head of the medical unit. NR and NKS helped in literature search, editing and proofreading the manuscript. All authors read and approved the final manuscript.

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