CASE REPORT

Aleukaemic leukaemia presenting with pathological fracture

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Accepted 6 June 2014

SUMMARY

A 19-month-old Chinese girl presented with pathological fracture of her right distal tibia. Peripheral blood revealed no abnormal cells, electrolytes were normal and bone biopsy at the fracture site only showed small aggregates of unremarkable lymphocytes. A bone marrow study could not provide a definitive diagnosis of acute leukaemia on morphology and immunohistochemistry. A diagnosis of precursor B-cell acute lymphoblastic leukaemia was unequivocally confirmed by a cytogenetic study which showed a hyperdiploid clone with gain of chromosome 4 among other trisomies.

BACKGROUND

Acute lymphoblastic leukaemia (ALL) is the commonest malignancy in children. It typically presents with fever, bleeding, malaise, lymphadenopathy and sometimes bone pain.¹ Pathological fracture was reported as an initial presentation in 5.7–12% of patients with ALL in childhood.² Cases reported in the literature all had either abnormal circulating leukaemic blasts or obvious bone marrow involvement and hence presented little diagnostic difficulty.^{2–6} This is the first case report of aleukaemic ALL presenting with pathological fracture in which neither bone biopsy nor bone marrow phenotype examination provided a definitive diagnosis.

CASE PRESENTATION

A 19-month-old Chinese girl with no significant medical or family history presented with painful swelling of her right leg and difficulty in weight bearing for 2 weeks. She remained afebrile and there was no history of trauma. She was initially managed conservatively with analgesics but the symptoms did not subside. Physical examination showed that the distal tibial region was swollen and tender. There was no pallor, signs of bleeding, skin lesions, lymphadenopathy or hepatosplenomegaly.

INVESTIGATIONS

Initial complete blood count showed a raised total white cell count of $16 \times 10^9/L$, an absolute neutrophil count of $7.8 \times 10^9/L$, an absolute lymphocyte count of $6.9 \times 10^9/L$, a haemoglobin concentration of 13 g/dL and a platelet count of $463 \times 10^9/L$. No abnormal white blood cells were seen on blood smear examination. Liver and renal function tests, alkaline phosphatase (308 U/L), calcium (2.65 mmol/L), phosphate (2.12 mmol/L) and lactate dehydrogenase (214 units/L) levels were normal. X-ray showed a pathological fracture of the right distal tibia with osteopenia of the surrounding

bones as well as radiolucent metaphyseal bands (figure 1). MRI of the lower limb demonstrated a bone marrow lesion in right distal tibia extending up to the middle third of the tibial shaft. Small soft tissue mass extending beyond the posterior cortex of the tibia was noted at the fracture site with rim of periosteal reaction around the lesion. Osteomyelitis and skeletal malignancies such as Ewing sarcoma and osteogenic sarcoma were suspected. A bone biopsy demonstrated no evidence of malignancy with only aggregates of small crushed lymphocytes shown. As haematological malignancy was not initially suspected, limited immunohistochemistry was performed. These lymphoid cells were shown to be positive for CD10, weakly positive for CD20 and negative for CD3, an immunophenotype that can be compatible with haematogones. Septic workup and bacterial cultures from the bone biopsy sample were unrevealing.

The patient developed neutropenic fever 4 days after the bone biopsy. A repeat complete blood count showed a normal total white cell count of $4 \times 10^9/L$ but the absolute neutrophil count dropped to zero. The haemoglobin concentration was 9.9 g/dL and the platelet count was $352 \times 10^9/L$. No blasts were seen in the peripheral blood smear.

A positron emission tomography-CT scan was performed to exclude any underlying malignancy, showing diffuse cortical thickening along the entire right tibial shaft. Bone marrow of the upper tibial shaft showed a higher fluorodeoxyglucose (FDG) uptake (SUVmax 1.6) than the contralateral side (SUVmax 1.3). However, there was only a low-grade FDG uptake (SUVmax 1.0) at the fracture site. No adjacent hypermetabolic soft tissue was detected. Overall findings were non-specific (figure 1).

Bone marrow aspiration and a trephine biopsy from bilateral iliac crests were performed to exclude a haematological malignancy. The aspirate was aparticle and no blasts were seen among the few nucleated cells present for microscopy; flow cytometric analysis was not performed. Trephine biopsy sections revealed aggregates of small lymphoid cells with condensed chromatin. However, the proportion of these cells could not be reliably quantified. Immunohistochemically, these lymphoid cells expressed B-lineage markers CD10, CD20 and CD79a and showed a precursor phenotype with terminal deoxynucleotidyl transferase (Tdt)-positivity. Other markers of immaturity, CD34 and CD99, were negative. Nearly half of the lymphoid cells showed positivity towards

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To cite: Chua GT, Chow KC, So JCC, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2014-204690

Figure 1 (Left) X-ray of right tibia showing pathological fracture of right distal tibia with osteopenia of surrounding bones as well as radiolucent metaphyseal bands. (Right) Positron emission tomography-CT scan showed diffuse cortical thickening along the entire right tibial shaft. The bone marrow of the upper shaft of right tibia demonstrates higher fluorodeoxyglucose (FDG) avidity (SUVmax 1.6) than the contralateral side (SUVmax 1.3). Fracture site only showed low-grade FDG uptake (SUVmax 1.0). Overall findings are non-specific.

proliferation marker Ki-67. Although Tdt-positive B precursors occurring in clusters are more likely to be leukaemic in nature than representing haematogones, definite exclusion of the latter is not possible based on phenotype. Subsequently, cytogenetic study revealed a hyperdiploid clone including trisomy 4 (karyotype: 53,XX,+X,+4,+6,+14,+21,inc[3]/46,XX[5]; [figure 2](#)), unequivocally demonstrating B-ALL in this patient. Examination of cerebrospinal fluid at diagnosis showed no evidence of central nervous system involvement.

DIFFERENTIAL DIAGNOSIS

Initial differential diagnoses in this patient in view of a pathological fracture and the X-ray findings were osteomyelitis, osteogenic sarcoma and Ewing sarcoma. However, the patient had no fever and blood cultures were negative. Bone biopsy showed no definite malignancy. With the subsequent development of neutropenia and anaemia, a haematological malignancy was highly suspected, in particular ALL. However, it was difficult to differentiate leukaemic blasts from haematogones due to the absence of blood involvement, atypical blast morphology and difficulty in quantifying the proportion of atypical or abnormal cells. The diagnosis was subsequently confirmed by the karyotypic findings. The distinction between lymphoblastic lymphoma with marrow involvement and leukaemia is arbitrary, depending on the extent of bone marrow and other nodal or extranodal involvements. In view of a more diffuse process not confined to the site of pathological fracture coupled with the presence of neutropenia and anaemia, ALL was a more appropriate diagnosis in this patient.

TREATMENT

The patient was initially managed conservatively for her pathological fracture with casting. After the diagnosis of ALL was performed, she was given induction chemotherapy according to the ALL-IC-BFM 2002 standard risk protocol, which consisted of intrathecal methotrexate, oral prednisolone, intravenous vincristine, daunorubicin and L-asparaginase. Further treatment was given accordingly.

OUTCOME AND FOLLOW-UP

Occasional blasts were seen in the peripheral blood on day 8 of prednisolone therapy. The day 15 bone marrow examination showed no increase in blasts and overall findings were consistent

with regenerating marrow postchemotherapy. Her neutropenia gradually recovered. Subsequent X-ray of the right tibia showed a healing fracture site. Bone marrow examination on day 33 showed normocellular bone marrow compatible with remission. The patient proceeded with the consolidation phase of chemotherapy.

DISCUSSION

ALL is the commonest childhood cancer, accounting for up to one-third of all paediatric malignancies.⁶ Common presentations include fever, bleeding, lymphadenopathy and hepatosplenomegaly, while about 30% of patients present with bone or joint pain.¹ However, musculoskeletal symptoms can be the only presenting feature of ALL, causing a delay in diagnosis. Kobayashi *et al* reviewed 16 patients with malignant lymphomas and ALL presenting with orthopaedic symptoms. None of them showed specific features of a malignancy, leading to a delay in diagnosis up to 20 weeks. Musculoskeletal manifestations include limping, joint pain at various sites and low back pain.⁷ Fractures have been reported as an initial presentation in 5.7–12% of childhood ALL, of which the spine is more commonly affected, compared with peripheral skeleton.² Radiological abnormalities are also common in children with ALL, but they are non-specific. These include osteopenia, lytic lesions, periosteal reactions, pathological fractures, sclerotic lesion and metaphyseal bands.⁷

Every ALL case reported in the literature had circulating blasts and/or presence of typical leukaemic blasts in bone marrow examination or in the fracture site biopsy, despite otherwise non-specific musculoskeletal presentations.^{2–9} However, the diagnostic challenges in this patient were the absence of a leukaemic picture and the atypical marrow blast morphology. This makes the distinction of ALL from an unusual proliferation of haematogones difficult and cytogenetic assessment became the critical step in supporting the final diagnosis.

Aleukaemic leukaemia is a rare presentation of leukaemia in which leukaemic blasts are absent in peripheral blood. Common published manifestations include leukaemia cutis or extramedullary granulocytic sarcomas. Leukaemia cutis refers to dermatological involvement showing multiple skin nodules, and lymphoblast infiltration is seen in biopsy.^{10–11} Extramedullary granulocytic sarcomas are commonly associated with acute leukaemia or chronic myelogenous leukaemia. Reported sites include pleura, breast and gingiva.^{11–13} Pathological fracture as a

Figure 2 (Left) H&E staining of second trephine biopsy showing the marrow was packed with small lymphoid cells with irregular nuclear contour, stippled chromatin and scanty cytoplasm. (Right upper) G-banded metaphase spread showing hyperdiploidy of leukaemic cells, including trisomy 4. (Right lower) Immunohistochemical staining showed positivity for CD10, CD20 and terminal deoxynucleotidyl transferase.

presenting symptom of aleukaemic leukaemia has yet to be reported.

Pathophysiology of musculoskeletal manifestations of ALL has been previously investigated. Halton *et al*¹⁴ and Boot *et al*¹⁵ studied 40 and 32 children diagnosed with ALL from Canada and the Netherlands, respectively. They mainly focused on bone mineral density and mineral profile. Both studies showed that most children with ALL at diagnosis had abnormalities in bone mineralisation, with normal bone mineral densities but reduced bone turnover. This was supported by the presence of low serum osteocalcin, serum procollagen type I C-terminal propeptide and urinary deoxypyridinoline, which are markers of bone formation; and carboxy-terminal telopeptide of type I collagen, which is a marker of bone resorption. Halton *et al*¹⁴ also showed that 1,25-dihydroxyvitamin D3 level was significantly low at diagnosis of ALL with associated hypercalciuria. These findings may be related to leukaemic infiltration of the bone marrow with marrow expansion. However, whether this is also applicable to aleukaemic leukaemia remains uncertain.

This case illustrates the importance of including acute leukaemia in the differential diagnosis of pathological fracture. It also demonstrates that unexplained cytopenias may be the first sign of acute leukaemia, before circulating blasts can be detected. Comprehensive investigations are needed and cytogenetic findings may offer important diagnostic information in addition to their well-recognised prognostic value. The clonal karyotypic changes confirm the leukaemic nature of the bone marrow B-cell precursors. The hyperdiploidy which includes trisomy 4 indicates a good prognosis and satisfactory response to anti-metabolite therapy. The estimated 5-year event-free survival is 85–95%.¹⁶

In summary, we reported the first paediatric case of ALL with aleukaemic leukaemia presenting with pathological fracture. Bone profile, including serum calcium, phosphate and alkaline

phosphatase levels, was normal. Clinical suspicion of haematological malignancy was warranted as a differential diagnosis in children presenting with pathological fracture. Early consultation with a paediatric oncologist and comprehensive investigations are crucial in reaching a correct diagnosis.

Learning points

- ▶ Acute lymphoblastic leukaemia (ALL) may present with pathological fracture with no circulating blast.
- ▶ A high index of suspicion of haematological malignancy is merited in a patient with pathological fracture, especially when the blood counts are abnormal.
- ▶ Early consultation with a paediatric oncologist and comprehensive investigation is crucial.
- ▶ Cytogenetic findings not only stratify risk and impact therapy in ALL, but may also help diagnose challenging cases.

Contributors All the authors have contributed substantially in conception and design, acquisition of data, and analysis and interpretation of data. All authors contributed in drafting and critical revision of the manuscript for important intellectual content. The authors also provided their final approval of the version published.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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