An intriguing case of B-acute lymphoblastic leukemia – addressing the diagnostic pitfalls

Jyotsna Yesodharan, Geeta Vidyadharan, Annie Jojo
From Department of Pathology, Amrita Institute of Medical Sciences, Kochi, India.

Correspondence to: Dr. JyotsnaYesodharan, 113, Sivaranjani, GCDA Colony, Thottakkattukara (P.O), Aluva, Kochi - 683108, Kerala, India. E-mail: jyotsnayesodharan@yahoo.co.in

ABSTRACT

Acute leukemia often presents with symptoms due to bone marrow failure. But with atypical presentations, the diagnosis may not be straightforward and requires thorough clinical examination followed by carefully selected and interpreted investigations. We present a case of acute leukemia in a child who was admitted with pain and swelling of foot. In absence of classical features, leukemia was not initially suspected and even on subsequent biopsy, the diagnosis could not be picked up, requiring thorough re-evaluation. We have hereby made an effort to analyse the pitfalls in this case to help practising clinicians and pathologists who might encounter similar scenarios.

Keywords: Acute lymphoblastic leukemia, Biopsy, Bone lesion, Child.

Leukemia is the most common childhood malignancy globally, wherein the overall proportion of leukemia in India ranges from 26.7% to 52.3% of all childhood cancers [1]. Though the diagnosis of acute leukemia is not very cumbersome with the help of routine investigations, difficulties arise when presentation is atypical, mimicking other diseases, as in our case. Our patient presented with a bone lesion in the extremity suspected to be osteomyelitis. Though osteoarticular symptoms are not very rare in acute leukemia, the radiological correlation is poor and hence a high index of suspicion is necessary to arrive at the diagnosis [2]. As we have noted on retrospective analysis of our case, routine and special investigations, unless carefully selected and interpreted in the light of possible differential diagnoses, can also mislead the clinician and pathologist. This results in undue delay in initiation of treatment. We intend to throw light on the initial diagnostic pitfalls in this case and improve awareness about these interpretative errors.

CASE HISTORY

A 4 year old female child, foreign national, presented to the local hospital with low grade fever of 2 weeks. She also had severe pain in the left foot making it difficult to bear weight and she was reluctant to walk for over a week. Her orthopedician noted tense tender swelling above the first metatarsal of left foot. Other systems were within normal limits.

Her haemoglobin level and total leucocyte count at that time were 8.8g/dL and 5900/mm$^3$ with C-reactive protein (CRP) of 8.13mg/L as noted in the discharge summary. X-ray and ultrasonography of left foot revealed cortical erosion at the base of first metatarsal. It was coupled with mildly increased vascularity and edema of adjacent soft tissue and was reported as osteomyelitis (Fig. 1). On subsequent MRI scan also, the possibility of infectious etiology, probably tuberculosis was suggested. She was posted for debridement and curettage from the bone lesion; the cheesy material obtained was sent for histopathological evaluation. Biopsy report from an outside laboratory service suggested a high grade primitive neuroectodermal tumor (PNET) / Ewing’s sarcoma. It was diagnosed based on the presence of neoplastic small round cells positive for vimentin, MIC2 (CD99) and focally for neuron specific enolase with Ki67 in 70-80% cells on immunohistochemistry. CD45, pancytokeratin, desmin, B-Acute lymphoblastic leukemia – diagnostic pitfalls

Figure 1: X-ray feet showing lytic lesion in (L) first metatarsal
synaptophysin and chromogranin were negative. Hence she presented to the Oncology department at our centre for further management.

At presentation in our centre, her routine blood counts revealed low haemoglobin - 5.7g/dL, total leucocyte count of 11520/mm$^3$, thrombocytopenia - 37000 platelets/mm$^3$ and CRP - 11.08mg/L. Serum calcium level was 10.18 mg/dL and LDH was 320 U/L. Peripheral smear revealed alarming 25% large atypical cells with blast morphology and bone marrow study was advised. Bone marrow study showed 96% blasts (Fig. 2) which on flow cytometry expressed CD19, CD20, CD22, CD10, HLA DR, CD34, CD38, CD86 and cytoplasmic CD79a suggestive of B- acute lymphoblastic leukemia (B-ALL). Subsequently, the bone curettage slides were reviewed and immunohistochemistry repeated which revealed positivity for CD99, CD20, Tdt and PAX5 with Ki 67 index of >90% in the small round cells (Fig.3). CD45, CD3 and synaptophysin were negative; hence reported as consistent with B-ALL.

She was initiated on chemotherapy with BFM ALL (Berlin-Frankfurt-Münster ALL) 2009 Protocol, an International collaborative treatment protocol for children and adolescents with ALL. The patient tolerated the treatment without major complaints and minimal residual disease (MRD) post induction was <0.01% of all leucocytes. She is continuing her treatment and is presently doing well.

DISCUSSION

Acute lymphoblastic leukemia is the most common paediatric haematological malignancy, 80-85% being of precursor B cell phenotype [3]. Most of the patients present with consequences of bone marrow failure like tiredness, pallor and purpura, fever with or without organomegaly and osteoarticular symptoms including pain, swelling or functional impairment.

Over 40% patients present with pain in their bones and seek orthopaedic help early in the course of the disease. Though this is frequently attributed to leukemic cell proliferation in marrow producing mass effect, the symptoms and radiographic changes often correlate poorly [2]. A variety of changes including osteopenia, lytic/ sclerotic/ mixed lesions, radiolucent metaphyseal bands, periosteal reaction, avascular osteonecrosis and pathological fractures have been described, though none is pathognomonic for leukemia.

These invite an array of differential diagnoses comprising inflammatory lesions like septic arthritis or osteomyelitis [4] as in our case as well as tumors like neuroblastoma, Ewing’s sarcoma/ PNET and rhabdomyosarcoma in children [5]. At this stage, a biopsy could help in distinction between inflammatory/ infective etiologies and malignancy, although ancillary studies like immunohistochemistry become mandatory in the latter, owing to the small round cell morphology in most of them.

In our case, in the context of clinical and radiological suspicion of osteomyelitis, initial bone biopsy report of malignancy came as a surprise. Though morphology confirmed a small round cell tumour, exact diagnosis of the entity could not be made. It highlights the need for clinical correlation as well as an extensive panel of immunohistochemical markers with awareness of variable antigen expression profiles in this confusing group of tumors. Here, the combination of CD45 negativity with MIC2 positivity might have misled the reporting pathologists making them drift away from diagnosis of a hematopoietic neoplasm.

Although CD45 is often used to exclude hematopoietic origin in undifferentiated tumors, it is important to remember that some cases of B-ALL/B-LBL (B-lymphoblastic lymphoma), acute myeloid leukemia (AML) cases of erythroid and megakaryocytic lineages as well as many mature hematopoietic tumors such as anaplastic large cell lymphomas, classical Hodgkin lymphomas and neoplasms with plasmacytic differentiation lack CD45 expression.

Hence, in cases of suspected B-ALL, TdT (preferably) or CD34 have been advocated to confirm the immaturity of cells and PAX-5 (preferably), CD79a or CD22 with CD10 to ascertain the lineage. CD20 used as common screening marker for B cell lineage is often negative or weak in B-ALL and CD19 lacks reliability on immunohistochemistry [6]. Olsen et al specifically observed that positive Tdt in ALL might help in distinction from Ewing’s sarcoma as both tumors can be CD45 negative and CD99 positive. Hence judicious use of markers and their careful
interpretation are absolutely essential for arriving at the right diagnosis.

Within a cohort of 493 cases diagnosed over 22 years, Kebudi R et al reported 5 cases of aggressive lymphoma/leukemia presenting as solitary bone tumor. All the 5 cases were initially diagnosed erroneously as Ewing’s sarcoma with a limited immunohistochemistry panel [7]. Ozdemirli et al also reported four cases of B-LBL presenting with localized intraosseous mass mimicking Ewing’s sarcoma clinically and histologically [8]. Thus, distinction between these entities can be difficult especially on small or crushed biopsy material. Hence complete immunophenotyping and wherever necessary, molecular studies are critical as the clinical behaviour and treatment are markedly different [9].

Bone changes in ALL are probably underreported as patients are subjected to imaging studies only in the presence of symptoms. Sinigaglia et al studied musculoskeletal manifestations of pediatric acute leukemias in 122 patients and noted that clinical localisation was mostly in extremities. Total 40.2% had radiographic changes at presentation and osteolysis was the commoner pattern (13.1%) though the overall prevalence of osteolytic lesions in ALL is low [4]. Most of these lesions localise in metaphysis of long bones, flat/ small bones may also be involved.

Though the pathogenesis is yet to be unravelled fully, osteoclast activation by parathyroid related protein (PTHrP) or the receptor activator of nuclear factor-kappa B ligand (RANKL) secreted by ALL cells is proposed. Mediators like transforming growth factor-beta, macrophage inflammatory protein-1a (MIP-1a) and inflammatory cytokines including interleukin (IL)-6, IL-3 and tumour necrosis factor have also been implicated [10]. The nutrients released from bones in turn, support tumor cell proliferation. Hence, osteoclast targeting agents and monoclonal antibodies against these mediators are prospective treatment options in these cases. However, the overall prognostic significance of osteolytic bone disease is still not clear [2].

CONCLUSION

In patients with atypical presentations, a high index of suspicion is necessary for early diagnosis of acute leukemia. Detailed history and examination along with preliminary hematological and biochemical investigations would give us useful clues. In the event of suspicious skeletal changes on imaging, as in our case, bone biopsy with carefully selected and interpreted immunohistochemistry panel and where indicated, molecular studies become essential to ensure appropriate therapy and predict prognosis.

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