Atypical presentation of acute myeloid leukemia with jugular venous thrombosis and multifocal osteomyelitis

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ABSTRACT
The patients with leukemia have a high risk of venous thromboembolism and rarely, multiple bone sites can be involved to present as multifocal osteomyelitis. A four year old child had cellulitis, multifocal osteomyelitis, left pneumonia with pleural effusion, cervical lymphadenopathy, hepatomegaly and left internal jugular vein thrombosis, finally diagnosed as acute myeloid leukemia. A timely bone marrow biopsy study should be considered in a child with deep vein thrombosis along with multifocal osteomyelitis to diagnose and intervene acute myeloid leukemia early.

Key Words: Jugular Venous Thrombosis, Multifocal Osteomyelitis, Acute myeloid leukemia.

Introduction
The risk of venous thromboembolism is four times higher in patients with malignancy but even more so in patients with lymphoma and leukemia.1,2 In a meta-analysis of cohort of 1752 children with acute leukemia from 17 prospective studies, the incidence of thrombotic complications was reported to be 5.2% (95% CI: 4.2-6.4).3 In another study, the incidence of venous thrombosis in leukemia was 4.39%.4 AML-M3 and non M3- AML can have thrombosis as a presenting symptom at diagnosis in 9.6% and 3.2% of cases respectively.5

AML presenting as multifocal osteomyelitis is uncommon.6 In AML, the infiltration of leukemic cells at multiple bone sites may mimic as multifocal osteomyelitis.6 In a retrospective study of 168 patients, bone lesions were seen in six patients with AML.7 We present a child with acute myeloid leukemia who at presentation had both multifocal osteomyelitis and jugular venous thrombosis.

Case report
A 4 year old boy from Karnataka, presented with complaints of fever along with right lower limb swelling for 2 months, swelling in left cheek for 1.5 months and swelling in the left side of the neck for 5 days. Fever was low grade, associated with loss of appetite with no history of progressive pallor, bleeding episodes, rashes, respiratory or gastrointestinal symptoms. Child had received IV antibiotics for two weeks; Ceftriaxone (100 mg/kg/day) for 7 days followed by Piperacillin-Tazobactam (300 mg/kg/day) and Amikacin (15 mg/kg/day) for 7 days and one unit packed red blood cell transfusion before admission to our hospital.

On examination, child was malnourished (Z score <3), pale, edema in left upper limb, swelling with tenderness over left zygoma (Fig. 1), significant lymphadenopathy in left cervical, right axillary, bilateral inguinal region, cellulitis over left shoulder (Fig. 1). Also there was swelling with tenderness over the upper third of right tibia with overlying cellulitis (Fig. 3). Liver was palpable 3 cm below right costal margin, had firm in consistency, smooth surface and round border; no splenomegaly. Bronchial breath sounds were present in the left upper zone of chest. Gradually child developed ascites and scrotal swelling, along with reduced air entry in left lung.

Investigations revealed Hemoglobin 8.2 g/dl, Total leukocyte count of 33,300 per cu mm with 75% polymorphs and Platelet count 1, 60,000 per cu mm. On admission CRP was >100mg/L and ESR 108 mm/hr. Peripheral smear done post transfusion shows normocytic normochromic blood picture with fragmented RBCs, neutrophilic leukocytosis containing toxic granules with adequate platelets. X-Ray of right lower limb reveals osteolytic metaphyseal lesion, narrow zone of transition with
multilayered type of periosteal reaction with no soft tissue involvement in upper third of right tibia, suggestive of osteomyelitis (Fig. 3). CT scan of Para nasal sinus showed thickened and sclerotic left maxilla with adjacent soft tissue thickening, suggestive of osteomyelitis. Chest X ray taken 5 days later showed left upper lobe consolidation which progressed as left lung consolidation with left sided mild pleural effusion confirmed by USG. Subsequent blood cultures showed no growth. USG neck showed multiple enlarged cervical lymph nodes with left internal jugular vein (IJV) thrombosis involving a large segment of left IJV and proximal part of left subclavian vein. Liver enzymes were normal with serum albumin 2.8 g/dl. HIV was negative. Nitro-blue tetrazolium test and TBNK (lymphocyte surface marker analysis) were negative. On day eleven of hospitalization, platelet count dropped to 36000 per cu. mm with rise of CRP>100 mg/dl.

In the meanwhile child received supportive care in the form of blood transfusions and pain management. Initial diagnosis of multifocal osteomyelitis was made and IV antibiotics started, to which child didn’t respond. In view of decreasing platelet count, fungal sepsis was suspected and antifungal drug was added. Child received low molecular weight heparin followed by warfarin for venous thrombosis. There was clinical deterioration in the form of progressive pneumonia, anasarca, persistent fever spikes and progression of the cellulitis. Bone marrow aspiration study shows many blasts (70%) which were medium to large in size with a high nucleus to cytoplasm ratio; moderate amount of basophilic cytoplasm. Nuclear indentation was noted in some of them with monocytoid appearance. 1-2 nuclei were seen in some of the blasts. Other marrow elements were decreased, suggestive of AML M5. Child was referred to Pediatric Oncologist for further management.

Discussion
Acute myeloid leukemia usually presents with non-specific symptoms like loss of weight, progressive pallor, fatigue, fever or bleeding episodes. Blast cells in peripheral smear clinch the diagnosis which can be further confirmed by bone marrow study. In this child, blast cells were missed in peripheral blood smear examination, probably because of post transfusion blood sampling. As the child was unresponsive to long duration of IV antibiotics, differential diagnosis of chronic recurrent multifocal osteomyelitis (CRMO)/ chronic non-infectious osteomyelitis was considered. Diagnosis of CRMO requires bone biopsy to rule out infection, neoplasm or Langerhans cell Histiocytosis. Finally bone marrow
aspiration was done for smear study and culture sensitivity which lead to diagnosis of AML-M5. Imberti et al reported two cases, of which first case was with AML M2 presenting as pulmonary thromboembolism and second case was with AML M4 presented with Deep vein thrombosis (DVT). Oehadian et. al also reported a case of AML M5 with DVT. 

Hypercoagulable state is a result of procoagulant activity of the blast cells of AML by multiple mechanisms including production of tissue factor and cancer procoagulant, along with other pro-inflammatory cytokines. Endothelium is directly and indirectly via cytokines converted from anticoagulant to procoagulant state. Stasis in blood flow can occur due to vascular channel narrowing by local growth of blast cells. Thus, all three components of Virchow’s triad are involved, thereby resulting in thromboembolic events in leukemia. In our case, the diagnosis was consistent with multifocal osteomyelitis, radiologically. Since the peripheral smear was consistent with infection, gram negative sepsis was considered and bone marrow aspiration study deferred in the beginning.

With the background of multifocal and multi-organ infection immunodeficiency was provisionally thought of and HIV was ruled out. Since chronic granulomatous disease can present with multifocal osteomyelitis, NBT test was performed to rule them out. Child was still having fever spikes in spite of 28 days of IV antibiotics and 4 blood cultures done with every step of hiking up of antibiotics yielded no growth of organisms. Hence bone marrow aspiration was planned for culture and smear study, which revealed AML M5.

A study reported that many leukemic children with bone lesions had clinical profile similar to infection or collagen vascular disease, thus delaying diagnosis. Two retrospective studies found that leukemic children with bony lesions were more often diagnosed late as ALL because these patients have mild anemia, low leukocyte count with few blast cells in the peripheral blood and a near normal platelet count. Our child had periostitis with osteolytic lesions in the metaphyseal region because of direct invasion of the marrow by the leukemic cells, and osteopenia due to high metabolic activity of the leukemic cells inside marrow spaces.

Hence, bone marrow biopsy study from the osteomyelitic site could have differentiated pathologically, if the osteolytic lesions were because of osteomyelitis or leukemic infiltrates.

In conclusion, AML should be considered in a child with deep vein thrombosis along with multifocal osteomyelitis and bone marrow biopsy should be done to rule out the possibility.

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References
Case Report

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