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ORIGINAL ARTICLE

An Uncommon Occurrence Of Acute Myeloid Leukemia In Tabriz

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ABSTRACT

Acute Myeloid Leukemia accounts about 80% of adult acute leukemias, that presents as de novo or following MDS. It shows typical clinical and cytological pattern of presentation, Hepatosplenomegaly presents in one third of the cases and Lymphadenopathy, extramedullary involvement are rarely seen. We tried to report an uncommon occurrence of AML in a 21 y/o female who admitted in Rheumatology service as a spondylitis. She experienced low back pain , anorexia , sever weight loss , fever, tenderness of lumbar spines and head of left humorous accumpanied with limited left shoulder girdle movements, and hematocytologic and pathologic challenges were not clear enough for specific diagnosis. The clinical and paraclinical findings of the case looked uncommon for de novo leukemia or MDS-AML. Even thought there were so many questions left without clear answer but the diagnosis of Acute Myeloid Leukemia confirmed histopathologically.

Keywords: Acute Myeloid Leukemia, Liver Dysfunction, Spondylitis

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Introduction

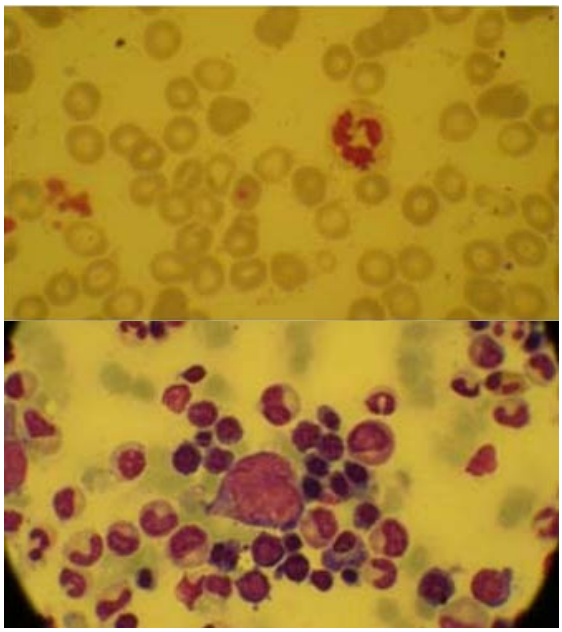
Acute myeloid leukaemia is a clonal, malignant disease of the haematopoietic tissue, which is characterized by the accumulation of abnormal (leukaemic) blast cells, principally in the bone marrow, and the impaired production of normal cells.[1] AML accounts for 80 percent of the acute leukaemias in adults[1]. The diagnosis of AML is based on the existence of 20 percent myeloblasts in the marrow nucleated cells. The common clinical manifestations at the time of presentation are fatigue, fever, weight loss and the signs and symptoms which are related to anaemia, thrombocytopaenia and neutropaenia.[1] Organomegaly (hepatomegaly and splenomegaly) occurs in approximately one third of the patients. Lymphadenopathy is extremely uncommon, except in the monocytic variant of AML.[1] Hepatic involvement has been rarely reported and the involvement is often in the setting of obstructive jaundice and the cholestatic pattern.[2],[3] Bone involvement in AML is rare too. Only in few case reports lytic bone lesions have been described.[2],[4],[5] This report describes the clinicopathologic findings in a patient which are extremely rare for an AML presentation.

Case Presentation

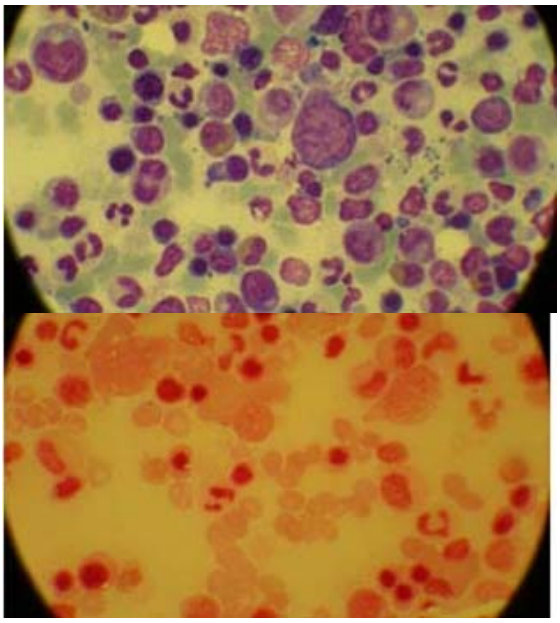
A 21 year – old woman presented with a history of lower back pain of 1.5 months duration in association with anorexia, weight loss and fever. The back pain was not radicular. The other symptoms were unremarkable. The patient was initially febrile (T: 39 ^{oc}). During physical examination, the positive signs included: conjunctival paleness, systolic murmur in the left sternal border, hepatosplenomegaly, tenderness in the lumbar vertebra and limitation in the left shoulder joint flexion with humerus head tenderness. The patient was admitted in the rheumatology service with the impression of spondylitis secondary to brucellosis or tuberculosis or malignancy and empirical antibiotic therapy

was started for the patient (ceftriaxon and vancomycin).Laboratory tests at the beginning were as below:
WBC = $8500\times10^3/\mu L$, Hb=7.8g/dL, PLT=$193\times10^3/\mu L$, ESR=67, CRP=++, retic count=1.2%, serum Iron=39µg/dL , TIBC=230 µg/dL, Ferritin = 710 ng/ml, LDH=1833U/L, AST=426 U/L, ALT=329U/L, Alkaline phosphatase=479 U/L ,Total Bil= 1.4 mg/dL, direct Bil=0.5 mg/dL, Albumin=2.1 g/dL, Hepatitis Serology= negative.

In imaging studies, abdominal and pelvic ultrasound showed hepatosplenomegaly and rernarkable fluid collection in the pelvis without paraaoritc lymphadenopathy. Spiral lumbar CT scan showed a lytic lesion in the L3 vertebra with destruction of the anterior cortex and the focal hypodensity in L3. MRI of the lumbar vertebra confirmed the abnormal signals in the L3 vertebrae. Plain radiography of the shoulder also revealed the decreased density of the humerus bone and the pathological fracture of the humerus. The biopsy of the L3 vertebra was performed. The pathology report showed scattered pleomorphic cells with hyperchromatic nuclei and a high nucleocytoplasnic ratio, which was suspective of malignancy. Considering the severe anaemia and the probability of the diagnosis of malignancy, oncologic consultation was requested, which was followed by marrow aspiration and biopsy. The peripheral blood smears showed unremarkable changes in the blood cells. Aspiration of the bone marrow revealed erythroid hyperplasia with megaloblastic changes and the presence of gigantoblasts, megakaryocytic hyperplasia with dysplastic maturation and decreased iron stores. Due to these changes, congenital dyserythropoietic anaemia or metastatic marrow was considered.


[Table/Fig 1]

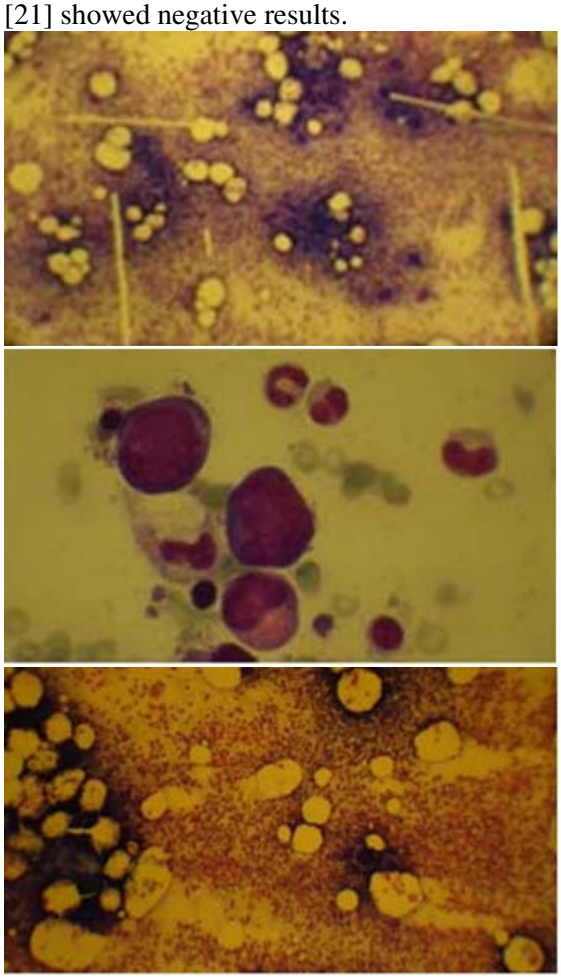
Marrow biopsy showed cellular marrow and increased megakaryocytes, but the erythroid and the myeloid series were intact. The most probable diagnosis was that of metastatic marrow or the unusual onset of AML-M7.
Despite receiving antibiotics and supportive care, the general condition of the patient deteriorated, and in two weeks, the biochemical tests showed the declining levels of the liver transaminases (ALT=204 U/L, AST=262 U/L).Due to the acute elevation of serum ALT and AST, the gastroenterologist did not agree with the liver biopsy performance Bone marrow aspiration and biopsy were repeated two weeks later. The neutrophil and platelet counts were normal, but anisopoikilocytosis and macroovalocytosis were seen in the RBCs. Marrow aspiration revealed hypercellularity, erythroid and megakaryocyte hyperplasia, megaloid changes in the erythroid and the myeloid series and the increase of blast cell numbers in some areas (5-6%). A diagnosis of acute nonlymphocytic leukaemia, most probably M6 or metastatic marrow was considered [Table/Fig 2].



[Table/Fig 2].

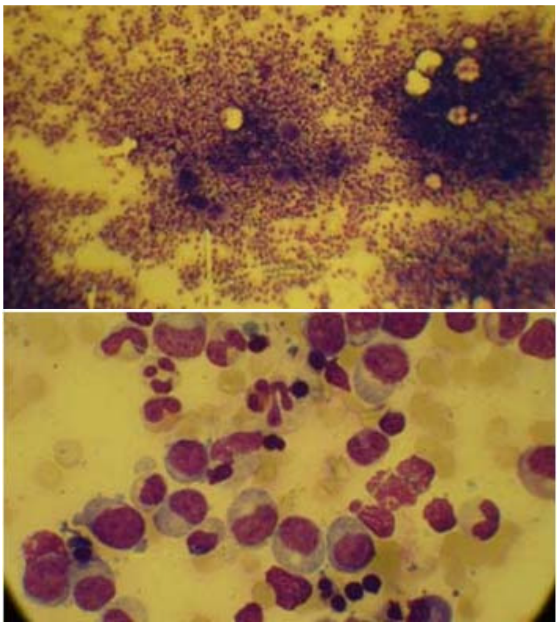
The pathologist reported that the marrow biopsy consisted of leukaemic infiltration. Then, the patient was transferred to the oncology service. At this time, the patient developed icteric sclera, distended abdomen and lower extremity oedema. The laboratory tests included: WBC= $3760\times10^3/\mu L$, Hb=7.7g/dl, PLT=$66\times10^3/\mu L$, Neutrophil count=2.6 $\times10^3/\mu L$, AST=190U/L ALT=79U/L, Alkaline Phosphatas=757 U/L, Total Bil=9.59 mg/dL, Direct Bil =5.63 mg/dL, LDH=1173U/L, Albumin=2.2U/L. Further, the ultrasound showed lymphadenopathy around the splenic vein and the head of the pancreas, splenomegaly and hepatomegaly and considerably free fluid collection in the abdomen and pelvis. Liver biopsy was performed and the pathological description revealed acute hepatitis, which was not confirmed by the second pathologist. The third peripheral blood smear demonstrated no changes in the RBCs and neutrophils, but the numbers of the platelets decreased and in the marrow aspirate, severe erythroid and myeloid hyperplasia with 5-6% myeloblasts and an increased number of megakaryocytes were seen. [Table/Fig 3].

The flowcytometry results showed the expression of the myeloid markers: CD14=48% CD13=65%, CD33=72%, CD34=13%, CD45=68% HLA-DR=62% CD11b=39% CD41=negative and glycophorin=negative. The molecular analysis for t [15], [17], inv [16] t (16, 16) and t [8], [21] showed negative results.



[Table/Fig 3]

The general condition of the patient was declined. In a few days, leukocyte, neutrophil and platelet counts decreased. Serum bilirubin reached the level of 12mg/dl and AST and ALT levels declined [28], [94] respectively). Another bone marrow aspirate showed decrease in the erythroid, myeloid and the megakaryocyte series, with an increase in the % of myeloblasts to more than 20%. So, the diagnosis of AML was confirmed. [Table/Fig 4]



[Table/Fig 4]

The examination of serial bone marrow aspirates in another center was described as follows:

First one: normal leukocyte and platelet counts in PBS and in the marrow aspirate, 60% cellularity with marked erythroid hyperplasia.

Second one: In PBS, neutrophils without hyper segmentation, normal platelet counts and ovalocytosis in the RBCs were seen. In the marrow aspirate, few myeloblasts were seen with severe erythroid hyperplasia. By Prussian blue staining, the iron stores were found to be low.

Third one: marrow cellularity was 65% with erythroid hyperplasia, 4-5% myeloblasts and increased numbers of megakaryocytes. In the last PBS, leukocyte and platelet counts were decreased and few myeloblasts were seen. Cellularity in the marrow aspirate was 65% and the erythroid and the megakaryocyte series were found to be decreased. Large and small myeloblasts were seen, which were characteristic of AML-M2. Due to the low performance status of the patient and marked elevation of the serum bilirubin, chemotherapy administration was impossible and she finally died due to sepsis.

Discussion

In this patient, the clinical and laboratory features were unusual for AML. Anaemia, thrombocytopaenia and neutropaenia are common findings in AML at the time of presentation.[1]Anaemia is a constant feature and thrombocytopaenia is nearly always present at the time of diagnosis. Neutropenia is also present in most of the patients.[1] This patient was anaemic at presentation. In spite of multiple packed cell transfusions and without any evidence of haemolysis, the anaemia did not resolve, other blood elements (platelets and leukocytes) were in normal limits until the end stage of the disease and finally at the end, the patient developed neutropaenia and thrombocytopaenia. During the sequential examination of the bone marrow aspirates, the myeloid series were not decreased and maturation arrest was not observed but the erythroid series were hyperplastic. Considering the morphological changes of the marrow cells and the low iron stores, myelodysplastic syndrome was not considered. Other unusual findings in this patient were significant for the elevation of liver transaminase, hepatomegaly and acsites at the time of presentation. AML patients rarely present with hepatic failure [2]. Liver involvement in AML is rare and often it occurs in the obstructive jaundice feature, secondary to granulocytic sarcoma[2],[3]. Only in one case report, hepatic involvement was reported with the features of transaminitis (73,49)[3]. In this patient, transaminase elevation was several times more than that of the normal limit. Considering negative hepatitis serology, this elevation remained ambiguous.

The pathology report revealed the sparing of the liver from leukaemic infiltration, but it was denied by the second pathologist's report. Gradually, the transaminases declined but they never reached the normal range. On the other hand, serum direct bilirubin rose in association with increase in the ascitic fluid. Hepatosplenomegaly is seen in one third of AML patients [1],[2], and ascites at the time of presentation is unusual. This patient initially presented with ascites that increased with the progression of the disease, despite albumin administration and other supportive treatments. Repeated abdominal ultrasound revealed paraaortic lymphadenopathy in addition to ascites, which is rare for AML.[1]The other unusual presentation in AML is lytic bone lesion, which rarely has been reported[2],[5] and also skeletal lytic lesion.[5] In the setting of the lymphoid

malignancy, osteolytic lesions have been described in ALL, NHL, CLL, HCL, MDS and Waldenstrom's disease[5]. Additionally, several case reports have described lytic lesions in association with acute megakaryocytic leukaemia. Our patient presented with a lytic lesion in the L3 vertebra and the head of humerus bone that led to a pathological fracture in the humerus head. But unfortunately, the L3 vertebra biopsy was not so helpful and confirmatory; the diagnosis through the mechanism leading to the lytic lesion in this patient remained obscure.

As this patient presented with anaemia, splenomegaly and mild hyperbilirubinaemia in association with hyperplasia and megaloblastic changes with gigantoblasts in the erythroid series, the diagnosis of congenital dyserythropoietic anaemia type I was proposed , but this impression was ruled out with the presentation of the lytic bone lesion, fever and progressive weight loss. AML-M6 was one of the differential diagnoses, but AML–M6a has 50% or more erythroid precursors in the nucleated population and 20% or more myeloblasts in the nonerythroid population of the marrow [2]. In the same way, AML-M6b was ruled out because the marrow cells did not contain 80% immature erythroid cells. Furthermore, in flowcytometry, erythroleukaemic markers (glycophorin) were not expressed by the marrow cells. In spite of the observation of more lytic bone lesions in AML-M7, morphological changes in the marrow aspirate cells and the cell markers in flowcytometry were not in favour of AML-M7.

The reason leading to the focus in this patient was the controversy over the explanation of the rheumatologist about the diagnosis and the management of the 21-year old weak woman with back pain, fever, fatigue and weight loss of two months duration that had become questionable initially for one medical student . At first, the patient presented in the setting of a rheumatological diseases, but the unique clinical and laboratory findings in this patient were unexplainable. Despite having long years of experience in the diagnosis and the treatment of haematological diseases, the sum of all these manifestations remained an uncertainty for our hematologists and hemopathologists. Although the consensus was AML diagnosis, answer to many questions remained ambiguous.

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