Case Report

Cyto-morphological features of extramedullary acute megakaryoblastic leukemia on fine needle aspiration and cerebrospinal fluid cytology: A case report

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Abstract

Extramedullary deposits may be the presenting feature of acute myeloid leukemia. An early and accurate diagnosis on cytology will aid in correct patient management. This is especially true for patients with acute megakaryoblastic leukemia (AML M7), where bone marrow aspiration may yield only a dry tap. While cytomorphological features of myeloid sarcoma of other types are well recognized due to its rarity, there are only two case reports discussing the morphological details of megakaryoblastic differentiation on aspiration cytology. We present the case of a 25-year-old patient with extramedullary involvement of lymph node and cerebrospinal fluid by AML M7, describing in detail, the morphological features on aspiration as well as exfoliative cytology.

Key words: AML M7, cytology, extramedullary, leukemia, megakaryoblastic, fine needle aspiration (FNA) cytology/biopsy (FNAC)/(FNAB)

INTRODUCTION

Acute megakaryoblastic leukemia (AML M7) is a rare hematological malignancy accounting for less than 5% of all cases of acute myeloid leukemia.[1] It is more common in children than in adults. AML M7 accounts for 7 to 10% of all cases of childhood AML but less than 1% of AML cases in adults.[2,3] It may occur as a complication in patients receiving chemotherapy for germ cell tumors.[4] Diagnosis is primarily based on bone marrow examination including both bone marrow aspiration and biopsy. Extramedullary infiltration is rare. There are only occasional case reports discussing the morphological features suggestive of megakaryocytic leukemia in extramedullary location on cytological smears.[5,6]

We report here a case of AML M7 presenting with cervical lymphadenopathy, emphasizing the cytological clues which may help in suspecting such a case on fine needle aspiration cytology (FNAC) and cerebrospinal fluid. This is also the first report describing the morphology of AML M7 in cerebrospinal fluid.
CASE REPORT

A 25-year-old male patient was treated with surgical excision for a mediastinal mixed germ cell tumor, the components of which included teratoma, embryonal carcinoma, and choriocarcinoma. Subsequently he was administered four cycles of BEP (bleomycin, etoposide, and carboplatin) and two cycles of etoposide and carboplatin in 2009. Six months after completing the treatment, he presented with complaints of easy fatigability and generalized weakness. On examination, the patient was found to have pallor. There was no lymphadenopathy, hepatosplenomegaly or any other abnormality. A clinical diagnosis of recurrent metastatic germ cell tumor was considered. A routine hemogram revealed hemoglobin of 6 g/dl. There was pancytopenia with a total leucocyte count of 3000/µl and a platelet count of 20,000/µl. Peripheral blood smear, however, showed no abnormal cells. A bone marrow tap done subsequently was dry. A bone marrow trephine biopsy and a touch preparation were done. The touch preparation showed few poorly preserved blasts, morphology of which was not clear. The decalcified sections of the biopsy were initially stained with hematoxylin and eosin stain and showed partial replacement of normal marrow by blasts. The blasts had scant to moderate cytoplasm with prominent nucleoli, a few of them being binucleate and a few multinucleated dysplastic megakaryocytes were also seen. On immunohistochemistry, the blasts were negative for myeloperoxidase (1:150 dilution, 59A5 clone, Novocastra, New Castle, United Kingdom) and leukocyte common antigen (1:100 dilution, Rp2/18 and Rp2/22 clone, Novocastra, New Castle, United Kingdom), but positive for CD 61 (1:100 dilution, 2f2 clone, Novocastra, New Castle, United Kingdom) [Figures 1a-c]. Based on these findings, a diagnosis of acute megakaryoblastic leukemia was made and the patient was treated for the same with daunorubicin and cytarabin. However, six months later, the patient developed a single large cervical lymph node measuring 4 × 4 cm. A fine needle aspiration (FNA) was done from the cervical swelling using a 23-G needle. The smears were fixed in 95% ethyl alcohol for Papanicolaou stain and immunocytochemistry, and air dried for May-Grünwald Giemsa (MGG) staining. Cerebrospinal fluid (CSF) was evaluated for the presence of blasts.

Cytomorphologic features

Microscopic examination of the aspiration smears revealed numerous blasts which varied in size from two to three times the size of mature lymphocytes. They had scant to moderate granular cytoplasm, fine chromatin, and single or multiple prominent nucleoli. Some of the blasts had a notch in the nuclear membrane; many had nuclear indentations and folds [Figure 2a]. Most of the cells were singly distributed. Interestingly at places, they were present in small clumps which on low power examination mimicked marrow particles as seen in smears prepared from bone marrow aspirate. Within this population, a few larger cells with moderate to abundant cytoplasm were identified. There were cells which had single nucleus, but with the nucleus showing lobations, indentations and folds, some being horseshoe shaped [Figures 3a-c]. Bi to multinucleated cells reminiscent of megakaryocytes were also noted [Figures 3d-f]. In addition, many anucleate pale blue staining masses were seen in the background, possibly representing shredded and clumped cytoplasmic fragments or giant platelets [Figure 2b]. Immunocytochemistry showed the blasts to be negative for MPO, but positive for CD61 and CD34 (1:100 dilution, QBEnd 10 clone, Dako, Glostrup, Denmark), thus confirming the diagnosis of extramedullary leukemic deposit of AML M7 [Figure 2c].

A cytocentrifuge preparation (Cytospin 4, Thermo Scientific, San Diego, USA) of the CSF specimen stained with MGG showed many blasts with scant to moderate granular cytoplasm, irregular nuclear margins, fine granular chromatin, and prominent nucleoli. There were binucleate forms (micromegakaryocytes) and multinucleate forms (immature megakaryocytes) [Figure 2d]. The patient was treated with three cycles of daunorubicin and cytarabin.

DISCUSSION

Extramedullary leukemic deposits often have to be differentiated clinically from infections and carcinomas for which FNAC is an important diagnostic tool. There are only a few studies describing the morphological features of acute leukemia on FNA smears, most of them being case reports.[5-21] However, of these, only one report discusses in detail the cytological features indicative of megakaryoblastic
differentiation.[5] We report the morphological features in a case of AML M7 with involvement of cervical lymphnode and cerebrospinal fluid. On FNAC, granulocytic sarcomas can be classified into blastic, immature, and maturing forms of leukemias, based on the proportion of blasts to the more differentiating granulocytic cells.[20,22]

Blasts from AML M7 typically show more abundant cytoplasm with a relatively lower nuclear to cytoplasmic ratio than what is seen in other subtypes of leukemia. In addition, they show granular cytoplasm and cytoplasmic blebbing.[5] Presence of blasts of varying sizes including both small and large blasts, focal clumping of blasts forming small groups may also indicate the possibility of megakaryocytic differentiation. Micromegakaryocytes in the form of large cells with single but multilobated nuclei, and/or bi or multinucleated cells having dusky cytoplasm or megakaryocytes along with dispersed giant platelets in the background may also be seen.

Although monoblasts also show nuclear membrane folds and indentations along with scant to moderate cytoplasm similar to megakaryocytes,[15] they lack other features like multinucleation, multilobation, cytoplasmic shedding, micromegakaryocytes, and giant platelets. Promyelocytes and promyeloblasts also show nuclear convolutions and low nucleo-cytoplasmic ratio, although some might have Auer rods. Kumar PV described many faggot cells (promyelocytes showing many Auer rods) in a case of granulocytic sarcoma diagnosed by FNAC.[7] Auer rods are however not seen in cases of AML M7. In the study by Suh et al, Auer rods were not seen in any of 27 cases of granulocytic sarcomas included in their study.[22] Another common differential is extramedullary hematopoiesis, especially when a deposit is characterized by presence of more maturing myeloid forms. A clinical history of myeloproliferative disorder or myelophthisic anemia, the presence of cells of erythroid lineage and also myeloid precursors besides megakaryoblasts can aid in making a correct diagnosis.[22] Metastatic carcinoma, when poorly differentiated, is an important differential diagnosis for AML M7 due to the presence of grouping of blasts, more abundant cytoplasm and large size of the blasts. Poorly differentiated carcinoma may, however, have a suggestive clinical history. Additionally, the tumor cells in carcinoma have coarser chromatin are more monomorphic and are cytokeratin positive on immunocytochemistry. Multinucleated giant cells, if present, will have more bizarre hyperchromatic nuclei with or without prominent nucleoli in contrast to megakaryoblasts. In the case under discussion since there was a history of a mediastinal germ cell tumor, metastasis from the same may also be considered as a differential both clinically as well as on morphological assessment. Of the germ cell tumors, seminoma especially shares some morphological features with leukemia/lymphoma infiltration as it is characterized by a hypercellular cytologic preparation with cells dispersed singly as well as in loosely dyscohesive clusters. The cells have scant to moderate occasionally vacuolated cytoplasm. Nuclei are round to oval with thin nuclear membrane, vesicular chromatin, and prominent one central nucleolus or two to three smaller nucleoli. Due to cytoplasmic fragility, bare nuclei are common place. However, the cells do not show cytoplasmic pseudopod formation. In contrast to megakaryoblastic leukemia which shows a more polymorphic population of cells of variable sizes with multinucleation and multilobation, multinucleated cells are usually absent in seminoma
except for occasional “syncytiotrophoblast-like” cells. Also background in the latter may have necrotic debris along with variable numbers of lymphocytes, plasma cells, and epithelioid histiocytes. A characteristic “tigroid” background may be noted on Romanowsky stains.[23] In comparison, AML M7 is more typified by presence of giant platelets and cytoplasmic fragments. Epithelioid histiocytes have not been typically associated with AML M7. However, some cases may be difficult to further characterize, in which case immunocytochemistry may be used. Seminoma cells are immunopositive for CD117, placental-like alkaline phosphatase (PLAP), and sometimes for cytokeratin, all of which are negative in a case of megakaryoblastic leukemia except for CD117 which may be focally positive. Embryonal carcinoma and choriocarcinoma usually do not share overlapping morphological features with leukemia. Smears in the former show mitotically active, markedly atypical cells arranged as glandular and papillary 3-dimensional structures.[24] Aspirates from choriocarcinoma show an admixture of multinucleated syncytiotrophoblasts and the mononuclear cytotrophoblasts in a background of hemorrhage and necrosis.[25] Although syncytiotrophoblasts may be misinterpreted for megakaryoblasts, they are much larger with more abundant cytoplasm, several pleomorphic nuclei and lack nuclear lobations. A metastatic malignant melanoma is a common differential for any undifferentiated malignancy. The tumor cells are mostly epithelioid-cell type, dispersed singly, having abundant cytoplasm; marked anisokaryosis, bi- and multinucleation are common. Nuclei are usually eccentrically placed and have prominent nucleoli. An important point of distinction is the presence of intranuclear pseudo-inclusions. Cytoplasmic melanin pigment, present only in a minority, is beyond doubt the most diagnostic. Confirmation in a case of amelanotic melanoma may be done with the aid of monoclonal antibodies for S-100 and HMB-45.[26] In morphologically ambiguous cases, a panel of antibodies including LCA, MPO, CD33, CD34, CD61, CD43, TdT, factor VIII, CD117, PLAP, S-100, HMB-45, and cytokeratin should help in arriving at the diagnosis.[16] Blasts in the present case were positive for CD61 and CD34. Suh and coauthors have used flow cytometry on their FNA material to characterize their cases of granulocytic sarcomas.[22] Farray et al. also have described a case of megakaryoblastic leukemia involving pleural cavity; they did not give detailed morphological description of the blasts though they performed a flow cytometry on pleural effusion fluid.[6]

In the cerebrospinal fluid sample evaluated in the present case, blasts, micromegakaryocytes and cells resembling megakaryocytes could all be identified as seen in the aspiration smears.

This is the first report describing the finer cytomorphological features suggestive of megakaryoblastic differentiation on both aspiration and effusion smears. The features highlighted here may be of help in diagnosis and subtyping of extramedullary leukemic deposits of AML M7, especially in the event of a dry bone marrow tap, which is a common problem.

COMPETING INTEREST STATEMENT BY ALL AUTHORS

The authors declare that they have no competing interests.

AUTHORSHIP STATEMENT BY ALL AUTHORS

All authors of this article declare that we qualify for authorship as defined by ICMJE. All authors are responsible for the conception of this study, participated in its design and coordination, and helped to draft the manuscript. All authors read and approved the final manuscript.

ETHICS STATEMENT BY ALL AUTHORS

As this is a case report without patient identifiers, approval from Institutional Review Board (IRB) is not required at our institution.

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