AML M7 Misdiagnosed as ALL

Jayashri Chaudhari · Antia Borges ·
Shweta Bansal · Pravin Mahajan

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Abstract Hematogones, which are normal precursors of B lymphocytes in the bone marrow, may be mistaken for blast cells on flow cytometry and histology when their numbers increase. We report such a case in a 16 months old male who was unsuccessfully treated for a pre-B cell ALL on the basis of flow cytometry of the bone marrow which showed a substantial population of CD19 and CD10 expressing ‘blast’ cells. A diagnosis of AML M7 was made on a subsequent bone marrow biopsy in which the blast cells expressed CD61 and Factor VIII, while they were negative for CD10 and CD20. Also present were a few CD10 and CD20 expressing small lymphoid cells, which were interpreted as hematogones. This report reiterates the problem of mistaking hematogones for ‘blast’ cells on flow cytometry, especially in the marrow of very young children where hematogones are often prominent.

Keywords Flow cytometry · Hematogones · AML M7 · Misdiagnosed

Introduction

We present a 16 months old male child with AML M7 misdiagnosed on flow cytometry as pre B ALL. Hematogones were interpreted as blasts cells. Hematogones are B lymphoid precursors that are normally seen in small children and many other neoplastic and nonneoplastic conditions. The immunophenotype of hematogones is similar to blast cells and they can be confused with blast cells on flow cytometry.

Method

A 16 months old male child was admitted to our hospital with a diagnosis of pre-B ALL that was refractory to treatment. The patient had received induction chemotherapy for pre-B ALL for 2 months.

A summary of the pretreatment investigations on which the diagnosis was made by the previous physician are as follows.

The hemoglobin was 5.4/dl the WBC count was 35,400/dl with 25 % blast cells on the peripheral smear. The bone marrow aspirate showed 52 % blast cells. Flow cytometry was done on the bone marrow aspirate and was reported as showing an acute lymphoblastic leukemia of pre-B type. A cytogenetic study on bone marrow aspirate showed a 48XY, t(4, 11) (q21, q23), +21, mar karyotype. Although the blast cells showed trisomy 21, karyotyping of normal cells was not carried out. So it is not clear whether the trisomy 21 was acquired or constitutional. The bone marrow trephine biopsy done before starting chemotherapy was reported as an acute leukemia of undetermined phenotype.

The patient presented to us with complains of fever, abdominal distension and skin rash. On examination the he

J. Chaudhari · A. Borges · P. Mahajan
Department of Pathology, S. L. Raheja Hospital and All India
Institute of Oncology, Mahim, Mumbai, Maharashtra 400012,
India

J. Chaudhari (✉)
Department of Pathology, Seth G. S. Medical College and KEM
Hospital, First floor, College Building, Parel,
Maharashtra 400012, India
e-mail: jayashreepath@yahoo.com

S. Bansal
Department of Oncology, S. L. Raheja Hospital and All India
Institute of Oncology, Mahim, Mumbai, Maharashtra 400012,
India

had an enlarged liver and spleen. The hemoglobin was 7 gm/dl; WBC count was 17,370/dl and the peripheral smear showed 3 % blast cells. The bone marrow aspirate was cellular and showed 60 % blast cells. A bone marrow trephine biopsy was done. It was hypercellular and was packed with large blast cells showing large vesicular nuclei with prominent nucleoli. They had abundant eosinophilic cytoplasm. Many multi-nucleated cells were noted. A few large cells showed multilobed nuclei resembling dysplastic megakaryocytes and very occasional normal megakaryocytes were seen. Also scanty small lymphoid cells were seen scattered throughout the marrow (Fig. 1).

On immunohistochemistry, the blast cells were positive for CD117, CD61, factor VIII (weak) and HLADR. They were negative for CD34, CD20, CD3, CD10, Tdt, MPO and Glycophorin C. The smaller lymphoid cells were positive for CD20, CD10 and Tdt. They were negative for CD34, CD3, MPO, CD117 and Glycophorin C. On the basis of these findings, the diagnosis of acute myeloid leukemia with megakaryocytic differentiation was made (Figs. 2, 3).

The pre-treatment bone marrow trephine biopsy was reviewed. The bone marrow was packed with two types of cells. The large cells showed large vesicular nuclei, prominent nucleoli and abundant cytoplasm. The smaller cells had small hyperchromatic nuclei with scanty cytoplasm. In comparison with our biopsy, the previous biopsy showed a greater number of smaller lymphoid cells. The larger cells expressed CD117 and were negative for CD34, Tdt, CD10, CD20, CD3, factor VIII, CD99 and Glycophorin C. The smaller cells expressed CD10 and a few expressed CD20. They were negative for CD34, Tdt, CD3, and CD99. The megakaryocytic marker CD61 had not been investigated. On review it was found to be expressed.

The patient was treated with high dose methotrexate and antibiotics based on his previous diagnosis. By the time the diagnosis of AML M7 was rendered, he was too ill for any further intervention and died of septicemia 23 days after admission.

Result and Discussion

Hematogones are normal precursors of B lymphoid cells. They are generally seen in infant marrows. Their number varies depending on the age of the child. As the age increases, hematogones decrease [1]. In certain conditions like iron deficiency anemia, idiopathic thrombocytopenia, neuroblastoma, regenerative marrow after chemotherapy lymphoma cytomegalovirus infection and post bone marrow transplant, they are increased [1–3]. The number may vary from <5 to more than fifty [1].

Morphologically, as well as on flow cytometry, hematogones show similarities with lymphoblasts [1] for which

Fig. 1 H & E stain. Pretreatment bone marrow biopsy showing large blast cells and smaller lymphoid cells. Shown at $\times 10$ original magnification

Fig. 2 Pretreatment bone marrow biopsy showing CD10 positive smaller lymphoid cells. Shown at $\times 10$ original magnification

Fig. 3 Post chemotherapy bone marrow biopsy showing CD61 positive blast cells. Shown at $\times 40$ at original magnification

they could be mistaken [2]. In comparison blast cells, hematogones have smaller condensed nuclei with indistinct nucleoli [2]. On flow cytometry, hematogones show maturation and show cells ranging from the most immature

Fig. 4 CD45 versus side scatter histogram. The population marked by arrow was gated

CD34 and Tdt expressing stage, to mature cells showing surface immunoglobulin. On the contrary blast cells show maturation arrest.

In this case, only one type of cell population was gated on flow cytometry (Fig. 4). These cells were CD19, CD10, HLADR and CD79a positive. They were negative for CD34, myeloid markers and megakaryocytic markers. Tdt expression was not studied in these cells.

We compared the flow cytometry result with IHC. The smaller cells in the biopsy showed the same features as the cells gated in the flow cytometry. Some of the smaller cells expressed CD20 indicating maturation. So the smaller cells most likely represent hematogones. As the smaller

lymphoid cells lack CD34 and Tdt expression, biphenotypic leukemia was excluded.

A similar case has been described in the past where acute megakaryocytic leukemia was misdiagnosed as ALL due to increased hematogones in the marrow [4]. To summarize, it is very important to correlate flow cytometry with blast morphology and all the cell populations should be gated during flow cytometry.

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