Pure Erythroleukemia (Variant Acute Myeloid Leukemia-vAML-M6) with Deletion of Chromosome 20, Mainly Presenting as Late Erythroblasts, a Unique Case Report with Review of Literature

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Abstract Acute erythroleukemia is characterized by a predominant immature erythroid population and accounts for approximately 2–5 % of all cases of acute leukemia. Two subtypes are recognized based on the presence or absence of a significant myeloid component: erythroleukemia and pure erythroid leukemia. Erythroleukemia is predominantly a disease of adults, while pure erythroid leukemia can be seen in any age including children. Here is a case of pure erythroleukemia presenting mainly as late erythroblasts which was diagnosed on bone marrow examination, cytochemistry and was confirmed on immunophenotyping. Possibly this is the only case so far demonstrating deletion of long arm of chromosome 20 in pure erythroleukemia.

Keywords Pure erythroleukemia · Late erythroblasts · Deletion 20q

Introduction

Acute erythroleukemia is characterized by a predominant immature erythroid population and accounts for approximately 2–5 % of all cases of acute leukemia [1]. Two subtypes are recognized based on the presence or absence of a significant myeloid component: erythroleukemia and pure erythroid leukemia. Erythroleukemia is predominantly a disease of adults, while pure erythroid leukemia can be seen in any age including children [2].

Here is a case of pure erythroleukemia presenting mainly as late erythroblasts which was diagnosed on bone marrow examination, cytochemistry and was confirmed on immunophenotyping. Possibly this is the only case so far demonstrating deletion of long arm of chromosome 20 in pure erythroleukemia.

Case Report

Fifty-six year old post menopausal women, non diabetic, hypertensive on erratic treatment was admitted for the complaints of easy fatigability 8 months and fever 4 months without any history of blood transfusion in the past or any significant family history. Patient was evaluated else were for the same complaints and had received iron infusion, vitamin B12, folic acid and antibiotics in the form inj cefepime, inj ceftriaxone, and oral fluconazole without any relief. Physical examination of the patient showed pallor, icterus, and temp of 101 °F and splenomegaly of 4 cms below left costal margin with rest of examination unremarkable. Investigations revealed as under:

Hb 4.9 gms/dl, TLC $1 \times 10^{12}/l$, DLC N30, L65, E2, BF3, platelets 021, Retics 0.1, PBF showed anisocytosis, macrocytosis and occasional NRBC. Liver and renal function tests were within normal limits. LDH 977 mg/dl. CXR and ECG were normal. Iron kinetics showed serum iron 170 µg/dl (37–145), TIBC 240 µg/dl (259–388) and transferrin saturation 70 % (13–37). Serum B12 levels were 11,325 pg/ml (211–911) after four injections of vitamin B12. Coagulogram was within normal limits. Brucella, Mantoux, HIV and PCR for TB were negative. Widal was negative. Gastroscopy revealed normal study. Anti CCP, ANA, RF, CRP were negative. Culture grew enterococcus sensitive to vancomycin. USG demonstrated

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Splenomegaly of 12.8 cms and grade I fatty liver. CECT showed right renal cortical cyst 1.5 × 1.5 cms with rest of the study normal.

Bone marrow aspiration (Fig. 1) was hypercellular showing mainly late erythroblasts with round nuclei. These erythroblasts mainly were showing moderate megaloblastosis. Cytoplasm was well hemoglobinized. There was mild dysplasia with some cells having bizarre nuclei. Megakaryocytes were dysplastic with abnormalities of segmentation of nucleus few micromegakaryocytes were seen. Diffuse PAS positive erythroblasts were seen (Fig. 2) and constituted 88 % of total cells. Myeloblasts constituted 5 %. markers revealed CD36, 21 % and Glycophorin A 86.80 % as positive and negative markers included CD45, CD34, CD5, CD19, CD33, CD13, CD15, CD117, CD41A, CD61, CD3 CY, CD71A CY, MPO. Cytogenetic studies revealed deletion of long chromosome 20 (Fig. 3). BM biopsy revealed scant marrow bit, however, showing replacement of marrow element by erythroid precursor cells, rest of cell lines are suppressed.

Treatment options were discussed and patient opted for supportive treatment only. Currently patient is receiving occasional packed red cell transfusion (Fig. 4).

Discussion

The subject of malignancies derived from erythroleukemia has been brought with controversies since its inception. Di Guglielmo [1] reported the original cases in 1917. In 1976 FAB classification defined erythroleukemia upon the overall percentage of myeloblasts. In 1985 FAB cooperative group revised its criteria by requiring at least 30 % of non erythrocytic elements to be type I or II blasts and defined

Fig. 1 Late erythroblasts

Fig. 2 Diffuse PAS positive erythroblasts

Fig. 3 Deletion of long chromosome 20

AML6 as a proliferation of >50 % erythroblasts and >30 % myeloblasts within non erythroid series [2]. WHO recognizes two subsets of AML-M6: erythroleukemia (erythroid myeloid leukemia) and pure erythroid leukemia. Erythroleukemia is defined by ≥ 50 erythroid precursors and ≥ 30 myeloblasts. Pure erythroid leukemia is defined by ≥ 80 % erythroid precursors. The established classification of acute erythroleukemia is partly based on the old FAB criteria and also upon morphological, cytochemical and immunophenotyping criteria [3].

One group has been actively researching the acute erythroleukemia since the late 1980s, during which time; classification has been developed and extensively published [4].

Fig. 4 BM biopsy

- Acute erythroleukemia, M6a (traditional FAB-M6, DiGuglielmo's syndrome, 1917).
- Acute erythroleukemia, M6b (pure erythroleukemia, DiGuglielmo's disease, 1926).
- Acute erythroleukemia, M6c (mixed erythroleukemia).

In rare cases the erythroid lineage is the only obvious component of an acute leukemia a myeloblast component is not apparent. The erythroid component consists predominantly or exclusively of proerythroblast and early basophilic erythroblasts. These cells may constitute 90 % or more of the marrow elements. Despite lack of myeloblast, these cases should be considered acute leukemia's. In a WHO proposal the blastic leukemia's that are limited to the erythroid series are designated pure erythroid malignancies.

Erythroleukemia (EL) is predominantly a disease of adults and the incidence ranges from 3 to 8 % [5–7]. Pure erythroleukemia is extremely rare and can occur at any age. The most known marker for EL has included glycophorin A and transferrin receptor (CD 71). However, glycophorin A has been reported completely negative in some cases of AML M6 probably it is a late erythroid marker, and CD 71 is a non specific activation marker which can be found in other AML. The platelet CD41 antigen and the myeloid markers as CD13 and CD33 can sometimes be positive. Probably the expression of Rh D antigen or of spectrin in AML6 could have some interest since they are expressed in immature erythroid cells [8]. Markers like beta-sialoglycoprotein, carbonic anhydrase 1, could be interesting tools to identify minimally differentiated M6. The most important role for antigenic erythroid markers is not in classical AML6, but rather to search for such a primitive erythroid phenotype among the acute undifferentiated leukemia. This entity of minimally differentiated erythroleukemia has been described as AML6 variant [9] and is now called 'pure erythroid leukemia' in the new WHO classification [10].

A large variety of cytochemical stains are available for characterization of erythroid lineage. The periodic acid Schiff (PAS) reaction is always negative in normal erythroid differentiation. Aberrant PAS positivity is observed in the pronormoblast and basophilic normoblast in AML-M6. Prussian blue stain demonstrates increased iron stores in AML-M6, sometimes with ringed sideroblast. Some authors reported occasional positivity of myeloperoxidase [11]. Pure erythroid leukemia—the undifferentiated form of pure erythroid leukemia is usually characterized by presence of medium to large erythroblasts usually with round nucleoli (proerythroblast); the cytoplasm is deeply basophilic, often agranular, PAS-positive. Occasionally, the blasts are smaller and resemble the lymphoblasts of ALL. The cells are negative for myeloperoxidase; they show reactivity with alpha naphthyl acetate esterase, acidic phosphatase, and PAS; the latter usually in block like staining pattern. In the bone marrow biopsies of pure acute erythroid leukemia, the cells appear undifferentiated [12].

Cytogenetics

Although numerous chromosomal abnormalities have been described in AML6, no consistent pattern has been specified. Clonal chromosomal abnormalities are found in 70–100 % of the patients. This heterogeneity probably reflects inclusions of secondary AML6 and therapy-related AML6 in some series. Loss of all or part of the long arm (q) of chromosomes 5 and/or 7 was observed with no difference in 65 % of de novo and secondary AML6. In only one series, the overall frequency of the abnormalities of chromosomes 5 and/or 7 observed in de novo M6 patients is similar to that observed in patients with therapy-related acute myeloid leukemia and substantially higher than that noted in patients with other types of AML de novo [13]. In every series, the incidence of patients with unfavorable karyotype is higher than other types of AML with inv 3;11q23;17 p abnormalities.

The karyotypes are often complex, with multiple abnormalities and sub clones. Using FISH, some cases of AML6 clearly demonstrated similar karyotypic abnormalities within both myeloid and erythroid cells. Atkinson et al. [13] proposes that a characteristic of this disease may be the presence of an altered primitive cell with features of both the erythroid and myeloid lineages.

Outcome

The outcome is classically poor than denovo AML6, treatment with intensive chemotherapy with anthracycline and cytosine arabinoside gives a complete remission rate (CR) of

about 62 %. In another series, the level of CR does not exceed 10–40 % especially in secondary AML6. CR, if obtained may be brief. The median survival is about 23 weeks. The survival is related to karyotype abnormalities. The allogenic bone marrow transplantation seems to be the best treatment for patients with abnormalities of 5q or 7q.

Prognosis

The outlook for AML6 patients is quite poor. The response to chemotherapy and the length of survival is dependent on many factors. The most important is karyotype abnormality [14]. The CR in patients with 5q or 7q abnormalities is about 20 % and median survival reaches 16 weeks compared to 77 weeks for patients without these abnormalities [15]. The difference of prognosis between de novo and secondary leukemia is related to karyotype abnormalities. The percentage of pronormoblast seems an important factor of survival according to Kowal-Vern et al. [16] with a mean survival of 34 months in AML6a, 3.5 months in AML6b and 10.5 months for AML6c. However, for other authors, more than the percentage of erythroblasts, cytogenetic abnormalities correlate with the rate of CR [13, 17–19]. Age is an important factor; older patients have a low CR and a short survival. Expression of *P*-glycoprotein is clearly a poor factor of survival [20]. The dismal outlook for these patients, particularly the M6b and M6c subtypes, may also be partially explained by frequent p53 mutations within the diagnostic bone marrow at initial diagnosis [21].

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