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Erythroid blast crisis in chronic myelogenous leukemia: Case report and review of literature

Rochelle Nagales Nagamos [a], Teresa Gentile [b], Neerja Vajpayee [a,*]

[a] Department of Pathology, SUNY Upstate Medical University, Syracuse, NY, United States
[b] Department of Internal Medicine, Division of Hematology-Oncology, SUNY Upstate Medical University, Syracuse, NY, United States

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ABSTRACT

Chronic myelogenous leukemia (CML) is a myeloproliferative disorder where over a period of time 15–20% of patients show blastic transformation with majority transforming into acute myeloid leukemia, most of which are of granulocytic lineage. Erythroid blast phase of CML is relatively rare with the incidence ranging from 0–10%. Further the incidence of acute erythroid leukemia by itself is fairly low amongst all acute leukemias. We report a case of 41-year-old patient with CML who failed to achieve cytogenetic remission, transformed to acute erythroid leukemia and eventually succumbed to the disease over a short period of time. Related literature is also reviewed

1. Case description

A 41-year-old woman prompted a visit to an optometrist due to blurred vision in June 2013, and was diagnosed to have retinal hemorrhage. Complete blood count revealed marked leukocytosis (326 K/μL), neutrophilia (25%, 64.6 K/μL) with a prominent myelocyte peak (27.5% myelocytes), basophilia (4.0%, 12.9 K/μL), and mild normocytic anemia (Hemoglobin 10.4 g/dl). Bone marrow study revealed hyperplastic myeloid series (myeloid/erythroid ratio of 8.1/1) with only 1.2% blasts. Further both karyotype and FISH analysis revealed presence of Philadelphia chromosome in nearly all cells (Fig. 1A and B) Based on these findings patient was diagnosed with Chronic myeloid leukemia (CML), chronic phase. She was started on Imatinib 400 mg daily and hydroxyurea. Despite achieving hematological remission three months after diagnosis, patient continued to have persistent cytogenetic disease as detected on follow up FISH assays with 32% cells showing t (9; 22). In June 2014, patient was switched to Nilotinib, as she appeared to have Imatinib resistant disease, although molecular testing for ABL kinase mutational analysis was negative. In July 2015 repeat blood work was done as patient complained of progressive fatigue and menorrhagia. CBC done at that time revealed a normal white cell count of 9.1 K/μL with 17.5% circulating blasts, (Fig. 1C) and hemoglobin of 7.5 g/dL. Bone marrow aspiration and biopsy was performed and the specimen was also submitted for flow cytometry and cytogenetic analysis. Prominent erythroid hyperplasia was noted on the bone marrow aspirate smears with 69.5% erythroid precursors, several of which showed dysplastic features (Fig. 1D–F). Although only 9% blasts were counted on the bone marrow differential count, flow cytometry revealed 14% cells in the blast gate (Fig. 1G) mostly expressing myeloid markers CD117, CD33, stem cell marker CD34 and with partial aberrant expression of lymphoid marker CD7. Bone marrow biopsy sections revealed marked architectural disarray with prominent erythroid hyperplasia (Fig. 1H) and normal number of megakaryocytes several of which were small and unilobed. Although no solid sheets of blasts were seen, CD34 highlighted scattered blasts throughout the biopsy section with a variable distribution estimated at approximately 10–15% (Fig. 1I). Both karyotype and FISH analysis revealed presence of Philadelphia chromosome. Additionally monosomy 7 was detected in 82% of the cells (Fig. 1J and K) and chromosome 3 anomaly was also noted. Based on the presence of marked erythroid hyperplasia (69.5%) and 9% bone marrow blasts the diagnostic criteria for acute erythroid/myeloid leukemia were met and a diagnosis of blast transformation of underlying CML to acute erythroid/myeloid leukemia was made.

Patient received 7+3 induction chemotherapy with Idarubicin and Cytoxan. Despite lowering of her peripheral blood counts patient continued to have persistent circulating peripheral blasts. She further developed subarachnoid hemorrhage, and septicemia and subsequently died six weeks after her hospitalization.

2. Discussion

Chronic myelogenous leukemia (CML) is a clonal disorder involving the pluripotent stem cell and is consistently associated

* Corresponding author.
E-mail addresses: Nagalesr@upstate.edu (R.N. Nagamos), GentileT@upstate.edu (T. Gentile), vajpayen@upstate.edu (N. Vajpayee).

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with the BCR-ABL1 fusion gene located on the Philadelphia chromosome [1]. The disease typically evolves in 3 distinct clinical stages: chronic and accelerated phases and blast crisis. In approximately 70% of cases, the blast lineage is myeloid, of which granulocytic and monocytic blasts are more common. The remaining 20–30% of cases show lymphoblast proliferation. Erythroid blast phase of CML is relatively rare and a literature review suggests that the incidence ranges from 0% to 10% [2].

Acute erythroid leukemia is a rare subtype ($< 5\%$) of acute myeloid leukemia that may arise de novo or from transformation of an underlying myelodysplastic syndrome. It is further subdivided into two subtypes namely: acute erythroleukemia and pure erythroid leukemia. Unlike pure erythroid leukemia in which the erythroid series is mostly comprised of proerythroblasts and

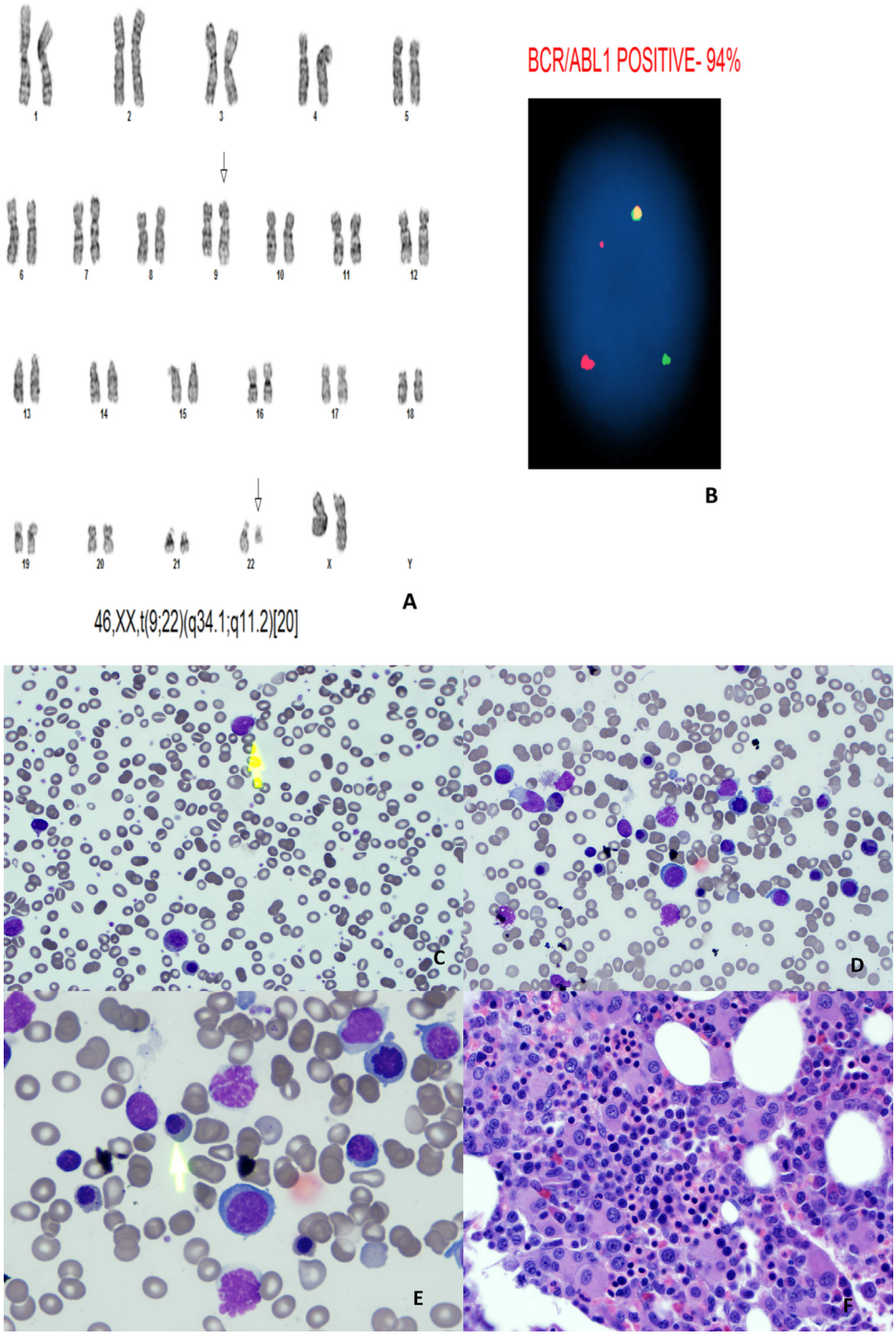

Fig. 1. A: Karyotype analysis depicting t (9; 22) at the time of initial diagnosis B: FISH for bcr-abl at the time of initial diagnosis. C: Peripheral blood with leukoerythroblastosis and circulating blast (arrow), Wright Giemsa Stain, 40x. D: Bone marrow aspirate smear with erythroid hyperplasia, Wright Giemsa stain, 40x. E: Dysplastic erythroid precursors few blasts, Wright-Giemsa stain, 50x. F: Hyper cellular bone marrow with hyperplastic and left shifted erythroid series, H&E, 40x. G: Bone marrow flow cytometry: increased population of CD33/CD34 positive bone marrow blasts. H: Glycophorin immunostain highlighting the hyperplastic and left shifted erythroid series, 50X. I: CD34 immunostain marks scattered blasts on the biopsy section, 50x. J: Karyotype analysis showing monosomy 7 in the blast phase. K: FISH for bcr-abl and monosomy 7 in the blast phase.

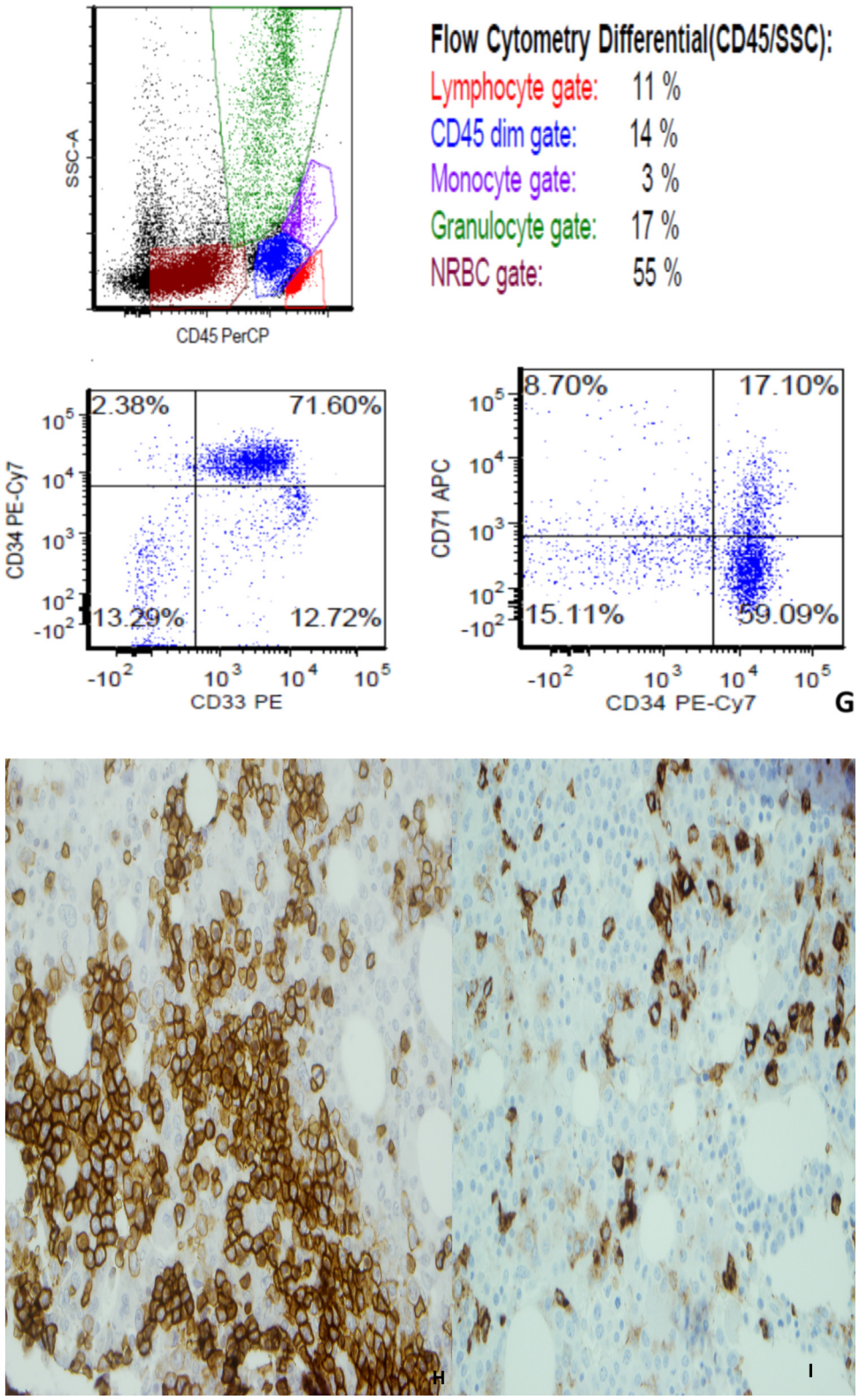

Fig. 1. (*continued*)

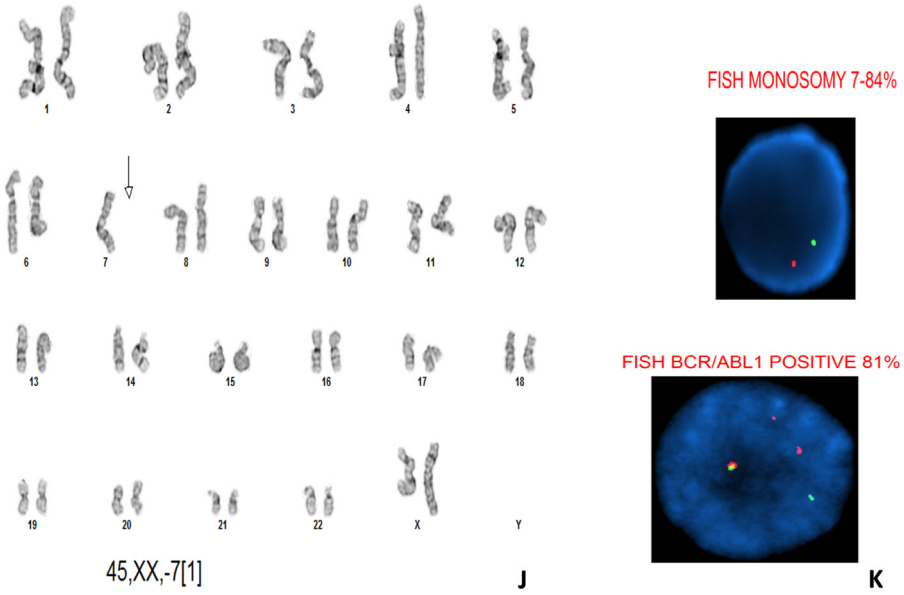

Fig. 1. (*continued*)

basophilic erythroblasts, in acute erythroleukemia (erythroid/myeloid) all maturation stages of the erythroid precursors are present (comprise > 50% of the entire nucleated cell population), may frequently show a shift to immaturity, are dyspoietic and myeloblasts comprise greater than 20% of non-erythroid cells [1].

Chronic myelogenous leukemia with erythroid crisis is a rare entity with variable reported incidence rates [2]. Based on our review of literature we came across very few reported cases of transformation of underlying CML to acute erythroid leukemia [3–8]. We also searched our institutional database for all cases of CML that transformed to acute leukemia over the course of last twenty years and did not find any other CML patient with erythroid blast crisis. Whether the criteria listed for diagnosis of erythroleukemia should be applied in CML erythroid blast phase is poorly defined. Some studies have considered the percentage of normoblasts below 50% as criteria for erythroblast phase but not erythroleukemia [6]. Although acute erythroid leukemia is far less common than CML erythroblast crisis, a few cases of Philadelphia-positive acute erythroid leukemia have been reported [5]. Studies have also suggested that erythroid blast phase is not independent of CML chronic phase. McFarlane and Tseih [6] were able to demonstrate a 'bcr-abl' fusion product in the normoblasts of CML, which provides concrete evidence confirming erythroid leukemia rather than a hyperplastic process. In our case at the time of disease progression in 2015 we were able to demonstrate presence of both bcr-abl fusion and monosomy 7 in majority of the bone marrow cells that on morphology were mostly erythroid precursors by FISH assays. Although the 9; 22 translocation was seen at the time of diagnosis, the anomalies of chromosome 7 and 3 were newly acquired in 2015, indicating karyotype evolution and disease progression. In the blastic phase of CML, several additional chromosome aberrations in addition to the Philadelphia chromosome have been reported in 75–80% of patients [3,5,7]. Complex rearrangements are widely dominant in acute erythroleukemia with clonal abnormalities mostly involving chromosomes 5 and 7 followed by 8, 16 and 21 [3]. There is no chromosome abnormality specific to erythroleukemia. In our patient we found anomalies of chromosomes 3 and 7 as her disease progressed.

pH-positive acute erythroid leukemia represents an even less common occurrence than erythroid blast phase CML. It is difficult to distinguish the erythroblast phase of CML from a pH-positive acute leukemia [9]. Although complex karyotype and presence of multiple chromosomal abnormalities is fairly common in all cases of acute erythroleukemia, very few cases of pH-positive erythroleukemia have been reported [5]. Blast phase of CML is often associated with a complex karyotype, including trisomy 8 and 19, double pH chromosomes, and isochromosome i (17q) [10,11]. The WHO classification does not specifically address the issue of erythroid hyperplasia in patients with CML or erythroid blast phase of CML. We feel due to presence of more than 50% erythroid precursors and increased myeloblasts (greater than 20% of the non-erythroid cells) our case meets the WHO diagnostic criteria for acute erythroleukemia (erythroid/myeloid). The criteria for diagnosing acute erythroleukemia arising from an underlying CML have not been firmly established, partly due to the rare occurrence of this phenomenon.

Chronic myelogenous leukemia blast crisis is highly refractory to standard induction chemotherapy, with a response rate of less than 20–30% [12,13]. In patient's with Imatinib resistant disease Dastanib and Nilotinib can help achieve hematological response however neither drug has been reported to be entirely effective in achieving complete cytogenetic remission or for treatment of blast crisis [14]. Further acute erythroid leukemia has an aggressive clinical course mostly with an adverse clinical outcome. Blast crisis with erythroblast phase is rare and remains a challenge to treat.

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