Human Pathology: Case Reports 8 (2017) 37–40

Contents lists available at ScienceDirect

Human Pathology: Case Reports

journal homepage: http://www.humanpathologycasereports.com

Case Report

Acute megakaryoblastic transformation from essential thrombocythemia

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ARTICLE INFO

Article history:
Received 12 March 2016
Received in revised form 7 August 2016
Accepted 22 September 2016

Keywords:
Essential thrombocythemia
Acute megakaryoblastic leukemia
Transformation

ABSTRACT

Essential thrombocythemia (ET) is a Philadelphia chromosome-negative myeloproliferative neoplasm characterized by sustained thrombocytosis. Its transformation into acute leukemia is a rare event (5% at 20 years). Transformation can be spontaneous or related to therapy. Acute leukemias most often associated with transformation from ET are myeloblastic or myelomonoblastic leukemias. There are very few case reports of ET transforming into acute megakaryoblastic leukemia. Here we report a case of transformation to acute megakaryoblastic leukemia in an elderly female patient who was treated with hydroxyurea for ten years. After 10-years with stable disease she presented and rapidly deteriorated with acute megakaryoblastic leukemia with high *JAK2V617F* mutant allele burden and high p53 expression. This case provides another example of the poor outcome of acute megakaryoblastic transformation of essential thrombocythemia.

1. Introduction

Essential thrombocythemia (ET) is characterized by persistent peripheral thrombocytosis, increased bone marrow megakaryocytes, splenomegaly and risk of both thrombotic and/or bleeding complications. ET is a *BCR-ABL1*-negative clonal myeloproliferative neoplasm (MPN) which carries more favorable prognosis than other MPN due to decreased incidence of thrombosis and less leukemic transformation (LT) [1–3]. Gangat et al., proposed a prognostic model for ET for its LT and survival with adverse features including age ≥ 60 years, leukocyte count ≥15×10^9/L, platelet count ≥1000×10^9/L and hemoglobin level less than normal [4]. They also showed a mortality rate of 90% in patients with LT, with median survival of 4 months. There was no difference in the survival benefit in patients with LT treated with intensive therapy or palliative therapy.

In MPN there is stem cell clonal myeloproliferation with mutations of Janus kinase 2 (*JAK2*), Calreticulin (*CALR*), or myeloproliferative leukemia virus oncogene (*MPL*) [5,6]. Unlike other *BCR-ABL1*-negative MPNs (polycythemia vera (PV), primary myelofibrosis (PMF) and prefibrotic PMF), 10–20% of ET patients lack *CALR*, *JAK2* or *MPL* mutations [5,7]. These cases of ET are known as triple-negative. In these cases the diagnosis heavily relies on the morphological assessment of the bone marrow and clinical assessment of secondary causes of sustained thrombocytosis.

The survival of patients with ET is near normal with 15-years survival of ~80% [8,9] and median survival of 20 years [10]. As with other MPNs, ET shares the characteristic of intrinsic propensity to progress to acute leukemia. The risk of progression to LT in these neoplasms may also be increased due to the treatment modalities used to either treat or control the symptoms of these patients. Drugs which can result in high incidence of leukemic transformation used in these patients include busulfan, P^{32}, chlorambucil, anagrelide and hydroxyurea. In the case of hydroxyurea, the existence and magnitude of such an increase in risk remains a subject of debate [11]. The risk of LT in ET is very low, from 0.7% to 9.3% in the first decade of the diagnosis. Rumi E et al., have shown that most of their patient with leukemic transformation had received cytoreductive therapy [7]. Long term follow-up study of these patients has shown that the disease becomes more aggressive beyond the first decade of diagnosis and the incidence of LT increases [12]. The aggressiveness of the disease may partially be due to acquisition of additional cytogenetic abnormalities at the time of LT which were not present at the time of chronic phase [4]. New cytogenetic abnormalities in LT may be acquired due to the treatment including hydroxyurea which is suggested to cause chromosome 17 abnormalities [13]. We are presenting a case of acute megakaryoblastic leukemic transformation of ET which is a rare evolution of this disease.

2. Case description

An 85-years old female diagnosed with *JAK2V617F* positive ET was treated with hydroxyurea and low dose aspirin for the past 10-years. Her symptoms were well controlled until 6 months before presentation when she started to have generalized fatigue and developed anorexia with significant weight loss. Three days prior to admission she

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http://dx.doi.org/10.1016/j.ehpc.2016.09.001

developed nausea but with no history of vomiting and other GI complaints. She has a past medical history of in situ squamous cell carcinoma with minimal invasion of the forearm and hand which was managed by surgical excision.

Physical examination had no significant findings apart from some sternal tenderness. Clinically there was no hepatosplenomegaly. Cardiovascular and respiratory systems examination was normal. During her admission in the hospital she developed shortness of breath and was started on levofloxacin for presumed pneumonia.

Her complete blood count (CBC) at the time of admission was Leukocytes 10.2 $\times$ 10^9/L (3.5–10.5), Neutrophils 5.71 $\times$ 10^9/L (2.0–7.5), Metamyelocytes 0.41 $\times$ 10^9/L, Myelocytes 0.10 $\times$ 10^9/L, Platelets 79 $\times$ 10^9/L (130–380), Hemoglobin 125 g/L (115–155) and no circulating blast cells were identified. Within a week her platelet count dropped to 32 $\times$ 10^9/L and hemoglobin dropped to 80 g/L and a few circulating blast cells with some large platelets noted (Fig. 1. A-B). Bone marrow aspiration was attempted however due to dry tap no aspirate material was obtained. The bone marrow biopsy showed hypercellular marrow (95% cellularity). There was decrease in normal hematopoiesis. The marrow was filled with sheets of blast cells (60% blasts) with scattered mitotic figures. Morphologically these cells ranged from large bizarre forms to smaller very dysplastic forms to less differentiated blast cells (Fig. 1. C-D). Dysplastic megakaryocytes were markedly increased with focally clustered and diffuse distribution. Reticulin staining showed mild to moderate reticulin fibrosis (WHO grade 2) (Fig. 1. E).

Immunohistochemical staining showed that most of the blasts expressed CD61 (Fig. 1. G) and CD42b (Fig. 1. H). The blasts were also positive for factor VIII-related antigen (FVIII) (not shown). The blasts showed variable expression of CD34 from weak to strong (Fig. 2. A). The megakaryocytes and blast cells also showed positivity for CD31 (Fig. 1. F). The megakaryoblasts were negative for myeloperoxidase, spectrin, CD3, CD20, pancytokeratin, and CD45. Staining for squamous cell marker (p40) and other cytokeratins (CD8/18, AE1.3, CK7, CK20) were also negative. Molecular studies performed on the formalin fixed, paraffin embedded (FFPE) bone marrow trephine biopsy after leukemic transformation showed mutation of *JAK2V617F*. The mutated *JAK2* allele burden at time of leukemic transformation was determined to be 61%. There were no mutations of *CALR* (exon 9) and *MPL* (W515L) identified on this sample. Due to the dry aspiration tap no sample for cytogenetics karyotyping was available. The results from

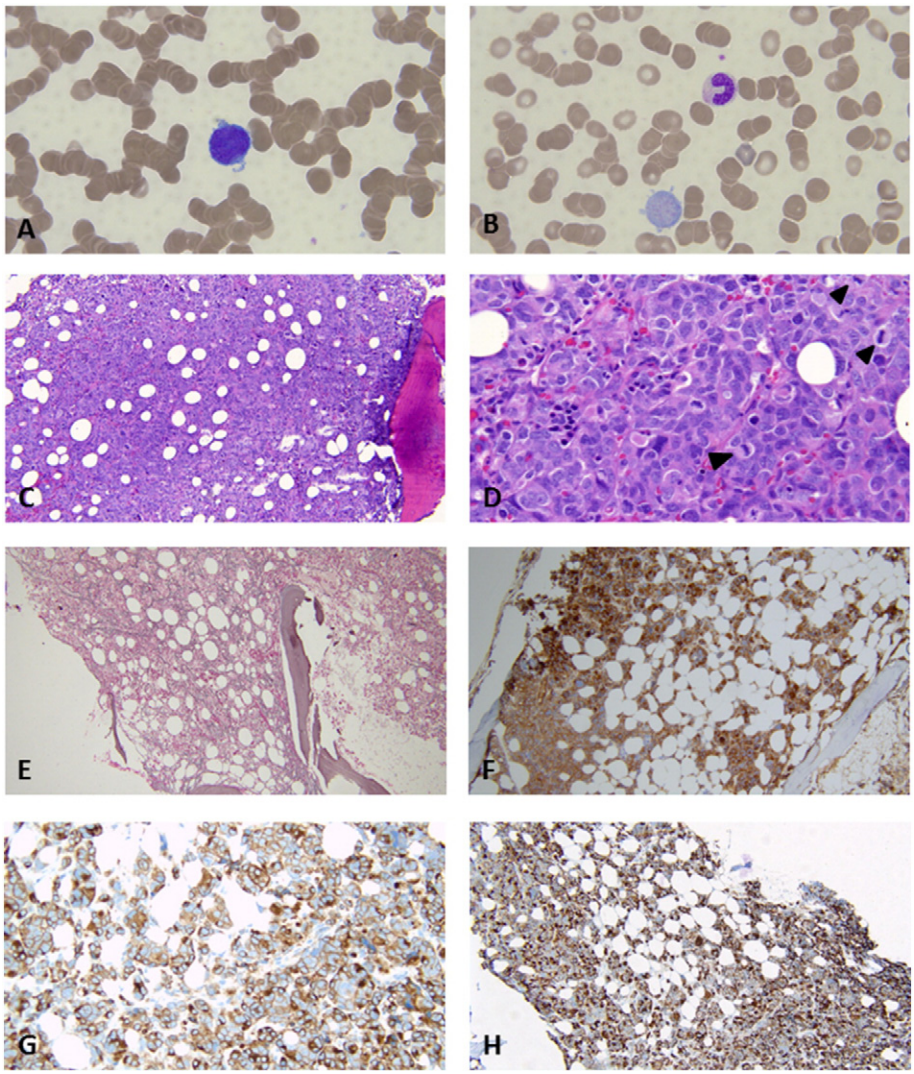

Fig. 1. (A–B) Peripheral blood smear. (A) Acute megakaryoblastic leukemia, circulating blast cell with prominent cytoplasmic blebs. (B) Circulating dysplastic large platelet (Wright-Giemsa, original magnification 40×). (C–H) Bone marrow core biopsy. (C) Hypercellular bone marrow showing increased immature megakaryocytic cells varying in size mixed with sheets of blast cells. (D) Frequent mitotic activity noted (arrow head). (Hematoxylin and eosin, original magnification 20× and 40×). (E) Mildly increased reticulin fibrosis (WHO grade 2) (Reticulin stain, original magnification 20×). (F) Mature and immature megakaryocytes were highlighted with CD31. There was complete replacement of marrow with CD31 positive cells (Original magnification 20×). (G–H) Megakaryocytes and immature cells of megakaryocytic lineage are highlighted by immunohistochemical stain for CD61 (G — Original magnification 40×) and CD42b (H – Original magnification 20×).