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Jacobs Journal of Hematology

Research Article

Two Cases with Essential Thrombocytopenia Transforming to Acute Myeloid Leukemia within a Short Time

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Received: 09-20-2015

Accepted: 09-30-2015

Published: 10-02-2015

Abstract

Myeloproliferative neoplasms (MN) are inclined to be transformed into acute myeloid leukemia (AML) / myelodysplastic syndrome (MDS) by losing the ability of differentiation as a result of neoplastic proliferation of hematopoietic cells with additional factors such as chromosome abnormalities and disorders of intracellular in time. Two cases with essential thrombocythemia (ET) transforming into AML within a short time are being presented for evaluation with current literature. Blastic transformation and acute leukemia should be taken into consideration and be examined in cases who have ET, leukocytosis, constitutional symptoms, decline in other cell lines, splenomegali at follow-up. If appropriate donor is found for transplantation, it should be planned after remision is obtained. Since prognosis is usually poor.

Keywords: Essential Thrombocythemia; Acute Myeloid Leukemia; Myeloproliferative Neoplasm; Transformation

Introduction

Myeloproliferative neoplasms (MN) are inclined to be transformed into acute myeloid leukemia (AML) / myelodysplastic syndrome (MDS) by losing the ability of differentiation as a result of neoplastic proliferation of hematopoietic cells with additional factors such as chromosome abnormalities and disorders of intracellular in time. Myeloproliferative neoplasms and myelodysplastic syndromes are sometimes seen together accompanied by myeloproliferative findings and cytopenia. Philadelphia-negative chronic myeloproliferative neoplasms (CML) are known in the forefront with essential thrombocythemia (ET), polycythemia vera (PV) and primary myelofibrosis (PMF) diseases. Morbidity and mortality rates were reported to have increased in cases with ET, but life expectancy is close to the normal population [1]. There are many causes of mortality, but the most serious cause is AML/MDS that is frequently seen with PMF and rarely with ET [2]. ET is diagnosed with thrombocytosis that is most prominent feature ruling out reactive thrombocytosis, MDS associated thrombocytosis and other MNs. In order to prevent thrombosis and bleeding cytoreductive therapy is administered high-risk patients. Life expectancy is generally close to the general population, but prognosis is very poor in patients with myelofibrosis conversion or transformation to AML [3]. AML transformation is not known exactly yet, cytoreductive therapy used in different treatments has been reported to be effective. Although hydroxyurea is commonly

used, there is no prospective randomized trial yet. Genetic aberrations (TET2, ASXL 1, CBL, IDH 1, IDH 2, EZH2, p53, Runx1) that are sometimes observed at stem cell level in ET can be observed in a single cell or different cell line series. In some sub-groups of patients, AML transformation may be seen in the linear clonally evolution containing given aberrations and different mutations. Two cases with essential thrombocythemia (ET) transforming into AML within a short time are being presented for evaluation with current literature.

Case1

A 53-year-old female patient had been diagnosed with ET in April 2013, and hydroxyurea - anagrelide combination therapy was administered. Leukocytosis and blasts were observed in the peripheral blood smear 6 months later. Further investigation with flow cytometry and immunohistochemistry staining of bone marrow biopsy was consistent with conversion for AML. Cytosine arabinoside and doxorubicin (7 + 3) had been administered and then remission had been achieved. She had received consolidation therapy with high-dose cytosine arabinoside. Allogeneic stem cell transplantation (ASCT) had been performed from his son who had complete HLA compliance five months later. Flow cytometry analysis of bone marrow samples revealed CD5: 3%; CD19: 85%; CD34: 24%; CD117: 16% that were compatible with complete remission after ASCT. Cytogenetic examination by FISHER resulted (chimerism analysis) in XY signal pattern in % 99.67 of cells (229 cells); XXI signal pattern in 0.33% of them (1 cell) 4 months after ASCT. Bone marrow biopsy was performed 11 months after the transplant, as mild cytopenia was observed (Leukocyte: 3.3 10e3/uL; neutrophil: 1.1 10e3/uL; hematocrit: 30%; hemoglobin: 10.7 g / dL; platelet: 49 10e3/uL; creatinine: 2,08 mg / dL). It was normocellular bone marrow and there were sufficient colonization and maturation findings without blastic cell in all three series with focal dishematopoiesis findings. Pancytopenia and blasts were seen in the peripheral blood smear at 16 months of follow-up post-transplant. AML recurrence had been confirmed by bone marrow biopsy and flow cytometry. Remission induction therapy has been initiated again and been continuing.

Case 2

A 65-year-old male patient had been diagnosed with ET in 2011 ruling out causes of reactive thrombocytosis and confirming positivity of janus kinase -2 (PCR JAK-2 V617F heterozygous mutant) by cytogenetic examination of bone marrow biopsy. Hydroxyurea had been initiated and then patient had been followed up. Five years later (February 2015), he had been referred to us with peripheral leukocytosis, pancytopenia, and the blasts (figure 1). AML had been confirmed by flow cytometry and bone marrow biopsy (Figure 2). Splenomegaly had been seen by ultrasonography. He had received 7+3 chemotherapy (cyclophosphamide and idarubicine) and then had been found to be unresponsive to treatment. He had been administered intermediate dose cytoxan (500 mg/m2/day) and idarubicine for re-induction. The patient died of sepsis on the eleventh day of treatment.

Figure1. Blasts in the blood smear of Case 2.

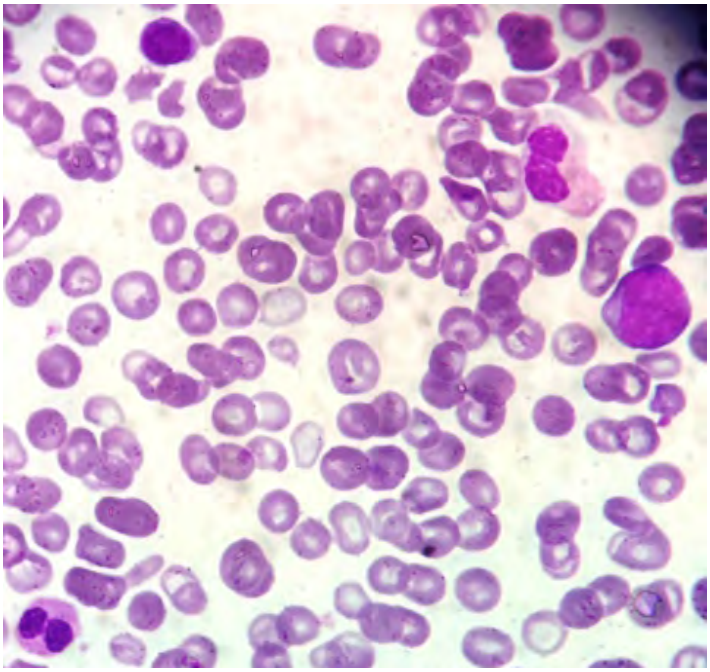
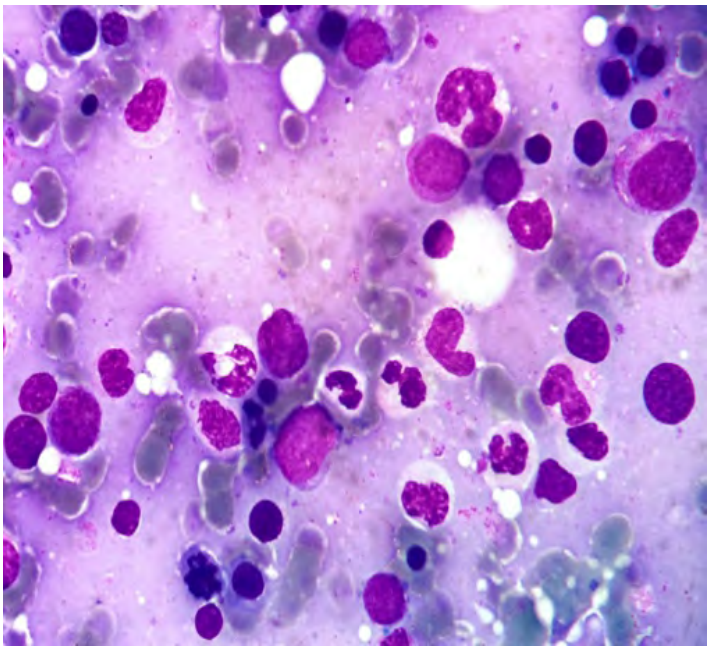


Figure2. Bone marrow view of Case 2 who had transformed to acute myeloid leukemia from essential thrombocythemia.



Discussion

Patients with ET have been reported to transform post-mye-

lofibrosis AML/MDS generally after 10-15 years according to literature [4]. AML conversion can be observed in long period. However, the transformation from ET to AML has been observed earlier. It has been suggested that genetic abnormalities, including reciprocal anomalies like t(1:15) and complex karyotype anomalies might facilitate AML transformation [4]. Especially busulfan, which is alkylating antineoplastic agent and radio phosphorus (P32) which is used in cytoreductive treatment is claimed to impair on 1, 7 and 17 chromosomes causing chromosome abnormalities that trigger the development of AML transformation [5]. In a study evaluating relationship between transformation and genetic changes in 89 patients, transformation was observed in 8 cases; there were de novo cytogenetic disorders during the transformation, developing de novo AML and der (1:7) was observed in AML pre-development stage, so the myelofibrosis phase in two cases who transformed from ET to myelofibrosis. Chromosome abnormality with der (1:7) has been reported to be related to poor prognosis and AML transformation as well [6]. In a study evaluating genetic variations in transformation from ET to AML by genome-wide SNP 6.0 array method in 29 patients, human granulocyte DNA has been investigated. Uniparental disomy (UPD) at chromosome regions and / or copy change has been observed in patients with ET that most of them were in chronic phase. Extra chromosome aberrations were detected in ET cases that transformed to either AML or myelofibrosis. In some cases, chromosome 9p aberration has been observed. Chromosome 5 and 7, or p17 aberrations have been reported to be related to AML transformation (OR 5.9; 95% CI 1.2-27.7, p = 0.006) and influence overall survival (HR: 18; 95% CI 1.9-164, P = 0.01). A genetic alteration has been confirmed in transformation from ET to AML with high resolution SNP array analysis of granulocyte DNA [7].

Our cases transformed to AML after six months that could be considered as a very short time. Only JAK2 mutation cytogenetic analysis by PCR as being a genetic analysis could be performed in our cases. Case 1 achieved remission after transplantation and blood counts recovered, but blastic transformation had been observed within a short time, approximately 1,5 years. Case 2 did not achieve remission and died within a short time due to comorbid diseases, such as diabetes mellitus, coronary artery disease, *etc*. and genetic abnormalities that were related to older age and cause resistance against chemotherapy.

There are few studies evaluating the impact of cytogenetic anomalies in ET on survival and transformation. In a study of 172 patients evaluated, 5.2% of the cases had cytogenetic abnormalities on admission and 1.2% of them acquired cytogenetic abnormalities during follow-up, but karyotype abnormalities have not been found to be the effect on survival [8]. Common chromosome abnormalities were reported to be on 9, 20, 5 chromosomes and also complex chromosomal abnormalities were observed in some cases. Cytogenetic tests were repeated during the follow-up of cases; myelofibrosis and AML/MDS were observed 2.9% and 1.2% of cases with normal karyotype, respectively (8). The intermittent cytogenetic analysis has not been recommended in ET; in case blood examination suggest a transformation, it may be performed [8].

In a study conducted in Sweden to assess the transformation of cases with myeloproliferative neoplasms to AML/MDS and the relationship between therapies and transformation, there was not found relation between the use of hydroxyurea and transformation; but P32 and other alkylating agents increase risk (Odds ratios: 4.6 and 3.4, respectively). Combination cytoreductive therapy (2 or more) has increased transformation risk in addition 2.9-fold more. It has been also reported that there was no drug exposure in 25% of patients who had an AML/ MDS transformation with conversion and unknown causes can take role in transformation with conversion as no drug exposure, different reasons could take a role [9].

In summary, it could be suggested that chemotherapy response is very poor in the transformation of the Philadelphia (Ph) -negative myeloproliferative neoplasms (MPN) to AML and survival is very short on the basis of our cases and literature. The treatment response rate was reported to be 54% in a study assessing 54 cases who had been treated with azacitidine due to chronic myeloproliferative neoplasms transformed to AML or MDS transformation without Ph [10].

Conclusion

Although AML transformation is rarely observed in cases with ET, acute leukemia transformation can develop within a short time in some cases. Blastic transformation and acute leukemia should be taken into consideration and be examined in cases who have ET, leukocytosis, constitutional symptoms, decline in other cell lines, splenomegali at follow-up. If appropriate donor is found for transplantation, it should be planned after remision is obtained. Since prognosis is usually poor.

Conflict of Interest

There is no conflict of interest.

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