"A Fatal Transformation": A Case Report on Essential Thrombocythemia Transformed to Acute Myelogenous Leukemia

"Ölümcül Bir Dönüşüm": Akut Miyelojenöz Lösemiye Dönüşen Esansiyel Trombositemi Üzerine Bir Vaka Raporu

Azliza Ibrahim[1], Alvin Oliver Payus[2]

[1] Department of Neurology, Hospital Pengajar Universiti Putra Malaysia, Persiaran Mardi - UPM, 43400 Serdang, Selangor, Malaysia
[2]Faculty of Medicine and Health Science, Universiti Malaysia Sabah (UMS), Jalan UMS, 88400 Kota Kinabalu, Sabah, Malaysia

ABSTRACT

Essential thrombocythemia is a benign myelodysplastic disorder. However, it can transform into a more malignant disorder such as acute myelogenous leukemia (AML). Here, we report a case of a 60-year-old lady diagnosed with essential thrombocythemia (JAK2 and BCR-ABL negative) and was treated with hydroxyurea. She also has comorbid disease of diabetes type II and bronchial asthma. She developed persistent pancytopenia and hydroxyurea was withheld since then. Repeated full blood picture analysis shows white cell of 6.3 x 10^9/L with 28% of leukemic blast cells. The blast showed negative staining with myeloperoxidase by immunostaining. Immunophenotyping of bone marrow aspirate shows presence of a blast population gated at CD45 and the cells are positive for immature markers of CD34, HLA DR, CD117, myeloid associated marker CD13 (bright), CD33 (heterogeneous), CD38 and CD71. Bone marrow BCR ABL analysis was undetectable. Based on these findings, the leukemic blast cells were classified as AML. Patient was given induction chemotherapy with daunorubicin (60 mg/m^2 per day for three days) and cytarabine (100 mg/m^2 per day for seven days). In conclusion, leukemic transformation can occur in essential thrombocytosis, and any eligible patients should be given chemotherapy as per protocol for AML.

Key Words: Essential thrombocythemia, leukemic transformation, pancytopenia, acute myelogenous leukemia

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ÖZET

Esansiyel trombositemi, iyi huylu bir miyelodisplastik hastalıktır. Ancak akut miyelojenöz lösemi (AML) gibi daha kötü huylu bir hastalığa dönüşebilir. Burada, esansiyel trombositemi tanısı almış (JAK2 ve BCR-ABL negatif) ve hidroksiüre ile tedavi edilmiş 60 yaşında bir bayan olgusunu sunuyoruz. Ayrıca, tip II diyabet ve bronşiyal astım komorbid hastalığı var. Kalıcı pansitopeni geliştirdi ve o zamandan beri hidroksiüre durduruldu. Tekrarlanan tam kan resmi analizi,% 28 lösemik blast hücreleri ile 6,3 x 109 / L'lik beyaz hücre gösterir. Patlama, immün boyamayla miyeloperoksidaz ile negatif boyama gösterdi. Kemik iliği aspiratının immünofenotiplemesi, CD45'e kapılanmış bir blast popülasyonunun varlığını gösterir ve hücreler, CD34, HLA DR, CD117, miyeloid ilişkili markör CD13 (parlak), CD33 (heterojen), CD38 ve CD71'in olgunlaşmamış markörleri için pozitiftir. Kemik iliği BCR ABL analizi tespit edilemezdi. Bu bulgulara dayanarak, lösemik blast hücreleri AML olarak sınıflandırıldı. Hastaya daunorubisin (üç gün boyunca günde 60 mg / m2) ve sitarabin (yedi gün boyunca günde 100 mg / m2) ile indüksiyon kemoterapisi verildi. Sonuç olarak, lösemik transformasyon esansiyel trombositozda meydana gelebilir ve uygun hastalara AML protokolüne göre kemoterapi verilmelidir.

Anahtar Sözcükler: Esansiyel trombositemi, lösemik transformasyon, pansitopeni, akut miyelojenöz lösemi

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ORCID IDs: A.I.0000-0001-9477-0871, A.O.P.0000-0003-4675-103X

Address for Correspondence / Yazışma Adresi: Alvin Oliver Payus, MD aculty of Medicine and Health Science, Universiti Malaysia Sabah (UMS), Jalan UMS, 88400 Kota Kinabalu, Sabah, Malaysia E-mail: dralvinpayus@ums.edu.my

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INTRODUCTION

Essential thrombocythemia (ET) is a common BCR-ABL negative myeloproliferative disorder involving hemopoietic stem cell especially megakaryocytic lineage. Haemorrhage and thrombocythemia are the main clinical manifestation (1). The diagnosis of ET is based on WHO criteria of sustained platelet count of ≥450 × 10^9/L; megakaryocytic proliferation with large and mature morphology in bone marrow biopsy; not meeting WHO criteria for other myeloproliferative disorder, myelodysplastic syndrome or myeloid neoplasm; and demonstration of JAK2V617F mutation or other clonal marker and no evidence of reactive thrombocytosis (2). In ET, 50-60% cases demonstrate of JAK2V617F mutation while 5-10% has MPL mutation. Recent studies show 60-80% cases with negative JAK2V617F/MPL has CALR mutation (gene encoding calreticulin) (3,4). ET is known to progress to acute myeloid leukaemia and post ET myelofibrosis with or without antecedent myelodysplastic syndrome (5). Apart from that, ET also has increased risk to develop other haematological malignancies such as non-Hodgkin's lymphoma and solid organ malignancies (6). The clinical course of ET is usually long, and the rate of blast transformation is very low compared with that chronic myeloid leukaemia, myelofibrosis and polycythaemia vera (7). The risk of leukemic transformation has been variable in several studies ranging from 1-4% during median follow up of seven to ten years (7-10). In this report, we will discuss on leukemic transformation in ET.

CASE REPORT

A 60-year-old woman was diagnosed as having ET, with an elevated platelet count of 1740 × 10^9/L and hyperplasia of megakaryocytes as determined by bone marrow aspiration. Trephine biopsy of the bone marrow was unsatisfactory and BCR-ABL analysis was undetectable. The platelet number was controlled at around 380-400 × 10^9/L while she was on treatment with oral hydroxyurea 1000mg once daily. During treatment, the hydroxyurea dose has been adjusted accordingly. The patient was noted to develop persistent thrombocythemia, which was associated with headache, high blood pressure, and giddiness. Clinically, there was no neurological deficit and computed tomography of the brain shows no intracranial bleeding. The repeated full blood picture shows white cell count of 6.3 x 10^9/L with 28% of leukemic blast cells. Bone marrow aspiration showed 52% of blast cells which is negative for peroxidase. A repeated molecular study shows negative for BCR-ABL. Immunophenotyping on bone marrow aspirate sample showed presence of a blast population gated at CD45 dim and moderate side scatter. The blast cells are positive for immature markers CD34, HLA-DR, CD117; myeloid associated marker CD13 (bright) and CD33 (heterogeneous). They are also positive for CD38 (heterogenous) and CD71. Trephine biopsy of the bone marrow shows marked reduction of all three hemopoietic cells with marrow infiltration by blasts (highlighted by CD34 and CD117) which appear moderate to large with moderate cytoplasm, open chromatin pattern and some with prominent nucleoli. The blasts are negative for CD3, CD20 and myeloperoxidase. Some mitotic figures and apoptotic cells were also seen. All the findings above were consistent with acute myeloid leukaemia, which occur in the background of ET. First cycle induction chemotherapy with daunorubicin (60 mg/m2 per day for three days) and cytarabine (100 mg/m2 per day for seven days) was started.

DISCUSSION

There is a large prospective study shows the leukemic transformation in ET independently increase with advance age, anaemia (7,11), platelet count ≥1000 × 10^9/l at diagnosis (7) and first decade of diagnosis (11). In this study, the risk of leukemic transformation (or myelofibrosis) also increases with hypercellularity and high reticulin content in bone marrow at diagnosis (11) and high white cell count. Early pre-fibrotic myelofibrosis has a greater risk of leukemic transformation compared to myelofibrosis. However, we did not observe any fibrosis in the bone marrow sample of our patient. In other study involving post ET/ polycythaemia vera myelofibrosis or primary myelofibrosis, the presence of platelet count of less than 50 × 10^9/l, bone marrow or peripheral blood blasts of more than 10% were identified as a leukemic transformation risk factor (12). In our patient, she developed persistent thrombocythemia and 52% of blast cells in the peripheral blood films, which could be the risk factors to the leukemic transformation.

Previous older studies have shown the association of cytoreductive agents such as melphalan (13), alkylating agents (10), radiophosphorus (9) and the use of more than one cytotoxic agent highly correlated with leukemic transformation. However, study by Wolanskyj et al (2005) (14) did not show any significant difference of leukemic transformation in group of patients with no cytoreduction, cytoreduction with non-leukemogenic agents (hydroxyurea, anagrelide or IFN) and agents believed to be leukemogenic (radiophosphorus, chlorambucil and/or busulfan). In current practice, alkylating agents and radiophosphorus are not a preferred agent due to possibility of leukemic transformation. There is no clear evidence that hydroxyurea or anagrelide are associated with leukemic transformation. In UK-PT1 study, the incidence of leukemic transformation was 1.2% in both treatment group of patients who were on anagrelide and hydroxyurea however the rate of transformation to myelofibrosis was higher in anagrelide group (15). Apart from that, Swedish study demonstrate that only a sequential use of greater than one cytoreductive agents will increase the risk of leukemic transformation by 2.9-fold (14). Therefore, the use of hydroxyurea in our patient has a very low risk factor to the transformation.

Myeloblast of greater than 20% in peripheral blood or bone marrow establish leukemic transformation diagnosis. In our patient, we found 28% of peripheral blast cells. It is important to rule out disseminated intravascular coagulopathy and complications such as infection, tumour lysis syndrome and hyperleukocytosis which should be managed as for AML. A few studies have evaluated the role of allogenic stem cell transplant (alloSCT) and curative chemotherapy in AML developing myeloproliferative neoplasm. Studies has shown that alloSCT and induction chemotherapy (idarubicin or liposomal daunorubicin and high dose cytarabine; anthracycline or fludarabine, and cytarabine) had significantly better overall survival. Induction chemotherapy resulted in complete remission and median progression free survival of five months. In Canadian study, curative intent (induction chemotherapy followed by alloSCT was significantly has higher overall survival compared to patients treated with non-curative intent. Besides that, patient who underwent alloSCT had significantly improved two- year overall survival compared to those who responded to induction therapy alone (16). In patient who are not eligible for intensive chemotherapy, studies have shown that hypo methylating agents may improve overall survival. In our patient, she was started on induction chemotherapy of cytarabine and daunorubicin, and will be assess for eligibility to undergo alloSCT.

CONCLUSION

Leukemic transformation can occur in ET despite having no fibrotic changes in the bone marrow. Any eligible patients should be treated with AML-induction chemotherapy followed by allogeneic stem cell transplant for long term disease control.

Conflict of interest

No conflict of interest was declared by the authors.

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