letter to the editor
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ACUTE MEGAKARYOBLASTIC TRANSFORMATION OF ESSENTIAL THROMBOCYTHEMIA

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Sir,

We read with interest the report by Messora *et al.*[1] on a case of myelodysplastic transformation of essential thrombocythemia following treatment with pipobroman.

Essential thrombocythemia (ET) is a chronic myeloproliferative disorder. It is a clonal disease that involves a pluripotent stem cell with the potential of progressing to myelofibrosis or, less frequently, to acute myeloid leukemia. Often cytotoxic agents are needed for a long time to reduce the platelet number in order to prevent thrombotic or hemorrhagic events.[2] Interferon[3] and anagrelide[4,5] seem to be effective and less toxic than the conventional drugs employed for ET, such as alkylating agents (e.g. busulphan), radioactive phosphorous (32P) and hydroxyurea (HU). Some of these last drugs (e.g. busulphan) may be involved in the rare leukemic transformation of ET. However, the literature contains reports of spontaneous leukemic transformation without previous cytotoxic treatment.[6]

We report the case of a 51-year-old man with ET who developed acute megakaryoblastic leukemia 55 months after diagnosis.

The patient, whose thrombocytosis was discovered by chance, was referred to our institution in January 1991. He was asymptomatic; physical examination was negative for hepatosplenomegaly. The blood count showed Hb 10.3 g/dL, WBC 7.7×10^9/L, platelets $1,065\times10^9$/L. Platelet ADP nucleotide was 1.0 μM/10^{11} platelets (n.v. 1.8-4.0). Both causes for reactive thrombocytosis and iron deficiency were ruled out. Bone marrow biopsy showed slight hypercellularity with numerous large megakaryocytes without fibrosis.

Karyotypic analysis was normal.

Diagnosis of ET was made according to *Polycythemia Vera Study Group* (PVSG) criteria.[7] Patient received low-dose busulphan until April 1991 (6 mg/day for 10 days in January and 2 mg/day for 20 days in March, 1991). The platelet count decreased to 700×10^9/L and this value was spontaneously maintained, so the patient was treated only with ticlopidine 250 mg/day. The patient was lost to follow-up by August 1993, when his condition was stable.

In July 1995 the patient was again referred to our institution for weakness and dyspnea. Physical examination was positive for II and III grade hepato- and splenomegaly, respectively. Blood count revealed: Hb 7.9 gr/dL, WBC 4.1×10^9/L (blast cells 52%), platelets 15×10^9/L and some megakaryocytic fragments were seen in the peripheral blood smear. Bone marrow biopsy documented a prevalence of dysplastic megakaryoblasts with mild fibrosis and blast cells with positivity for monoclonal antibodies against the coagulant factor VIII-related antigen.

Bone marrow immunophenotypic characterization demonstrated positivity for CD34, CD13, CD 33, HLA-DR, CD117, MPO7 and CD41a in the blast cell population. The karyotype was normal in 1 out of 20 observed metaphases, while 19 cells showed a 43,XY, del (5)(q31;q35), t(7;13)(q22;q22), –15, –18, –22 karyotype.

A diagnosis of acute megakaryocytic leukemia was made and the patient was treated with the ICE (idarubicin, cytarabine and etoposide) protocol; however, he died suddenly after 1 day of therapy and autopsy revealed an acute myocardial infarction.

Megakaryocytic leukemia is a very rare disease

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that represents 3-12% of acute myeloid leukemias; however, its incidence may be much higher when it occurs as a transformation from a prior myeloproliferative disorder.[8] There are many data regarding AML related to therapy (t-AML) with alkylating agents such as busulphan; moreover, a relationship to dosage has been demonstrated in leukemogenesis.[9] Balanced and unbalanced non random chromosome aberrations have been observed in t-AML, in particular deletion or loss of whole chromosomes 5 and 7.[10]

Althoug our patient was treated with low doses of busulphan, he showed a megakaryoblastic transformation associated to cytogenetic abnormalities. Therefore the acute phase could have been related to the progression of a malignant clone responsible for ET, without any significant role being played by prior therapy.

References

1. Messora C, Bensi L, Vanzanelli P, Temperani P, Carotenuto M, Sacchi S. Myelodysplastic transformation in a case of essential thrombocythemia treated with pipobroman. Haematologica 1996; 81:51-3.
2. Cortellazzo S, Viero P,Finazzi G, D'Emilio A, Rodeghiero F, Barbui T. Incidence and risk factors for thrombotic complications in a historical cohort of 100 patients with essential thrombocythemia. J Clin Oncol 1990; 80:556-62.
3. Turri D, Mitra ME, Di Trapani R, Lipari MG, Perricone R, Cajozzo A. Alpha-interferon in polycythemia vera and essential thrombocythemia. Haematologica 1991; 76:75-7.
4. Mazzucconi MG, De Sanctis V, Chistolini A, Dragoni F, Mandelli F. Therapy with anagrelide in patients affected by essential thrombocythemia: preliminary results. Haematologica 1992; 77:315-7.
5. Balduini CL, Bertolino G, Noris P, Ascari E. Effect of anagrelide on platelet count and function in patients with thrombocytosis and myeloproliferative disorders. Haematologica 1992; 77: 40-3.
6. Hattori A, Nagayama R, Kishi K, et al. Primary thrombocythemia in Japan: a survey of 225 patients. Leuk Lymphoma 1991; 4:177-86.
7. Murphy S, Hiland D, Rosenthal D, Lazlo J. Essential thrombocythemia: an interim report from the Polycythemia Vera Study Group. Semin Hematol 1986; 23:177-82.
8. Hoffmann R, Benz EJ, Shattil SJ, Furie B, Cohen HJ, Silberstai LE. Haematology: basic principles and practice. 2nd ed. New York:Churchill Livingstone, 1995.
9. Pedersen-Bjergaard J, Larsen SO, Struck J, et al. Risk of therapy-related leukemia and preleukemia after Hodgkin's disease. Lancet 1987; 3:83-8.
10. Pedersen-Bjergaard J, Rowley JD. The balanced and unbalanced chromosome aberration of acute myeloid leukemia may develop in different ways and may contribute differently to malignant transformation. Blood 1994; 83:2780-6.