short report
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TRISOMY 13 IN A CASE OF MYELOFIBROSIS WITH MYELOID METAPLASIA WITH EARLY BLASTIC TRANSFORMATION

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ABSTRACT

We describe a case of early myeloid blastic transformation in a 64-year-old man suffering from myelofibrosis with myeloid metaplasia. Both chronic and blastic phase cytogenetic analysis showed trisomy 13 to be the sole chromosome aberration. A potential role for this rare abnormality in determining such an unusually poor clinical outcome is discussed.

Key words: trisomy 13, myelofibrosis with myeloid metaplasia

Trisomy 13 is a rare cytogenetic aberration that preferentially interfere with myeloid proliferation and differentiation.[1] It has been documented mostly in acute myeloid leukemia (AML), less frequently in myelodysplastic syndromes (MDS), while it is extremely rare in chronic myeloproliferative disorders (CMPD).[2] Trisomy 13 has been associated with adverse prognostic significance in both AML and MDS.[2]

Here we describe a case of early blastic transformation in a patient with myelofibrosis with myeloid metaplasia (MMM) in whom karyotypic analysis revealed trisomy 13 to be the sole cytogenetic abnormality in both chronic and blastic phase.

Case report

A 64-year-old man was admitted into our hospital in February 1994 because of fatigue, abdominal discomfort and early satiety. The patientís previous history showed no severe illnesses or any exposure to mutagens. Physical examination revealed considerable splenomegaly (spleen was palpable 11 cm below the left costal margin). A routine blood count showed: hemoglobin 10.2 g/dL, white cell count 49×10^9/L; differential: neutrophils 6%, eosinophils 1%, basophils 3%, lymphocytes 2%, monocytes 1%, metamyelocytes 13%, myelocytes 11%, promyelocytes 6%, myeloblasts 2%; and platelets 112×10^9/L. A small number of erythroblasts were also observed. Red blood cell morphology was markedly abnormal for the presence of many distorted and tear drop-shaped erythrocytes. Bone marrow biopsy and aspiration demonstrated increased fibrosis and dense hypercellularity due to intense granulocytic hyperplasia with 3% myeloblasts. No dysplastic changes were observed in the granulocytic or erythroid lineages, excluding myelodysplasia with myelofibrosis. On the basis of these findings, a diagnosis of MMM was made. The patient was started on hydroxyurea with steady control of leukocytosis. However, during the following months several blood transfusions were administered for progressively worsening anemia. In July 1994 the patient required hospitalization for fever, night sweats, progressive anemia, splenomegaly, and bleeding. Peripheral blood count showed a dramatic rise in the white cell count (120×10^9/L with 56% myeloblasts), hemoglobin 6.0 g/dL, platelets 12×10^9/L. Bone

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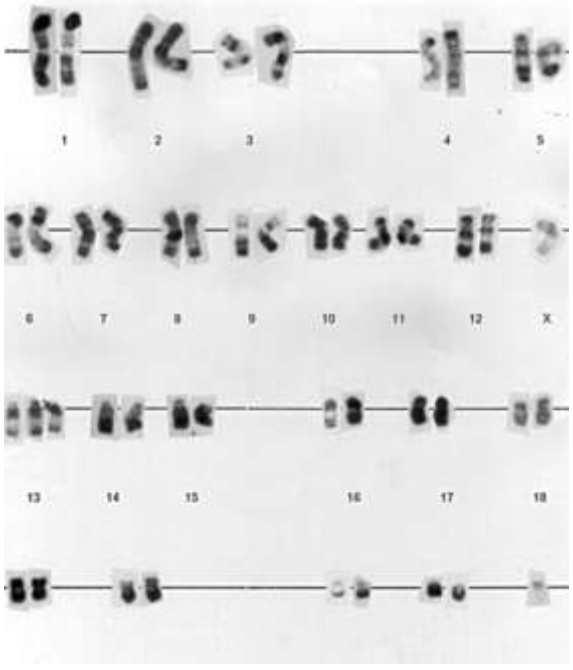

Figure 1. Patient karyotype: 47,XY,+13 (RHG banding).

marrow aspirate revealed a 60% infiltration of myeloid blast cells. Immunophenotypic analysis, performed on bone marrow mononuclear cells as previously described,[3] indicated positivity for CD13, CD33, CD15, CD11b, and HLA-DR antigens. Three courses of cytosine arabinoside (ARA-C) and 6-thioguanine (6-TG) were administered, yielding a reduction of splenomegaly and leukocytosis and an improvement in the clinical status; however, in December 1994 the patient died from severe cerebral hemorrhage in a setting of disease progression.

Cytogenetic analysis was performed on bone marrow cells using both the direct method as well as 24h unstimulated cultures of fresh heparinized bone marrow. Metaphases were analyzed by RHG banding. At diagnosis 60 metaphases were examined: 48/60 showed a 47,XY,+13 karyotype (Figure 1) and 12/60 were 46,XY. This suggested an acquired clonal abnormality in an individual with a normal constitutional karyotype. In July 1994, when blastic myeloid transformation was clearly diagnosed, trisomy 13 was once again the sole cytogenetic abnormality found in 37 out of 43 metaphases, while 6/43 metaphases were 46,XY.

Bone marrow was investigated for evidence of a BCR/ABL chimeric gene; neither p210 nor p190 BCR/ABL fusion transcripts were detected, thus effectively excluding Ph-negative chronic myeloid leukemia.[4]

Discussion

There are two related aspects of special interest in this case: the unusually early onset of myeloid blastic transformation in a patient with MMM and the presence of a chromosomal abnormality that is extremely rare in CMPD. Even though the onset of signs of disease may precede diagnosis by months or years in MMM, median survival from the time of diagnosis is approximately 5 years and acute leukemic transformation occurs in about 5 % of cases following a durable chronic phase.[5] Of interest, cytogenetic aberrations have been shown to exert considerable adverse prognostic weight.[6]

In our patient myeloid blastic transformation was documented 7 months from the time of diagnosis; we hypothesize a pivotal role for trisomy 13 in determining this unusually unfavorable clinical outcome in a CMPD, although the abnormal karyotype clone did not undergo expansion at the time of the blastic phase. An early leukemic progression of myelodysplasia was recently reported in a patient with trisomy 13 as the sole cytogenetic abnormality.[7] In addition, in AML trisomy 13 has been associated with adverse clinical significance in terms of both complete remission achievement and duration.[2] The role that the additional copy of chromosome 13 plays in the pathogenesis of different myeloid neoplasms is unknown.

Trisomy 13 usually arises in an early stem cell that retains the potential for myeloid and lymphoid differentiation, as demonstrated by its documentation in myelodysplastic and myeloproliferative disorders as well as in secondary, bi-phenotypic, and undifferentiated acute leukemia.[2,8]

Flt3/Klk2, a gene encoding for a receptor-type tyrosine kinase mapped on chromosome 13 to 13q12 in humans, is thought to have a role in regulating pluripotent stem cells and early

progenitor cells.[9] In addition, the soluble form of the ligand for the murine Flt3/Flk2 gene has been shown to stimulate human bone marrow cells that are highly enriched in stem cells and primitive uncommitted progenitor cells.[10] On the basis of these data, one may speculate about a gene dosage effect in originating clones with aberrant growth capacity by interacting with mechanisms of stem cell renewal and differentiation in both MDS and CMPD. Further characterization of molecular changes in hematological malignancies with trisomy 13 are expected to define more exactly the role of single genes in determining the origin and progression of these neoplasms.

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