Chronic Myeloid Leukemia Evolving after Idiopathic Myelofibrosis

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The chronic myeloproliferative disorders were first grouped together by Damashek [1] in 1951. Although they were initially regarded as inter-related entities, the later discovery of the Philadelphia chromosome and the peculiar molecular and cytogenetic findings related to chronic myeloid leukemia separated this disease from the others.

Although CML has been reported in patients with preexisting "Philadelphia-negative" chronic myeloproliferative disorders, it is a rare occurrence. It has been seen in polycythemia vera [2] and in essential thrombocythemia [3], but not until now in a patient with idiopathic myelofibrosis.

Patient Description

In 1996, a 41 year old Caucasian male patient with an unremarkable medical history presented with mild anemia and arthralgia. Physical examination was normal but a blood count revealed hemoglobin of 10.9 g/dl, white blood cells 5.73 x 109/L and platelets 846 x 109/L. Differential revealed 64% neutrophils, 24% lymphocytes, 5% monocytes, 3% eosinophils, 1% stabs, 1% metamyelocytes, 1% myelocytes and 1% basophils. There were also occasional blast cells and nucleated red cells. Marked red cell anisopoikilocytosis with teardrop forms and basophilic stippling was present. No fragments were obtained on bone marrow aspiration and a trephine biopsy showed evidence of a chronic myeloproliferative disorder with markedly increased and abnormal megakaryocytes and severe collagenic myelofibrosis and osteosclerosis. Karyotype analysis was normal and analysis by polymerase chain reaction for the BCR/ABL transcript on peripheral blood was negative.

The patient was treated with anagrelide, which succeeded in reducing the platelet count to around 400 x 10^9/L and for a long period he was largely asymptomatic. The spleen, which was initially impalpable, gradually enlarged to become palpable 5–6 cm below the left costal margin. The hemoglobin level remained around 10 g/dl and WBC below 10 x 10^9/L.

Nine years after the initial diagnosis, WBC began to rise and reached 67.74 x 10^9/L with a differential of 3% blast cells, 1% promyelocytes, 10% myelocytes, 8% stabs, 63% neutrophils, 5% lymphocytes, 4% monocytes and 1% basophils. Hemoglobin was 9.4 g/dl and platelets 298 x 10^9/L. This was accompanied by an increase in the size of the spleen to be palpable 12 cm below the left costal margin.

Analysis for the BCR/ABL transcript by PCR was positive and the translocation involving the ABL and BCR genes was seen on fluorescent *in situ* hybridization. A cytogenetic examination of bone marrow metaphases demonstrated a reciprocal translocation of chromosome 9 and 22 in most cells examined. PCR for JAK2 V617F and the newly described cMpl mutations W515L and W515K [4] were negative (kindly examined by T. Lasho at the Mayo Clinic, Rochester, MN, USA).

The patient was then treated for chronic myeloid leukemia with standard doses of imatinib (400 mg per day). After 3 weeks he developed severe neutropenia and thrombocytopenia, which necessitated reduction and eventual cessation of imatinib therapy. This was later resumed and doses were gradually increased again to 400 mg/day. After 3 months a 2 log reduction was found in the BCR/ABL transcript as detected by a quantitative PCR. The spleen was also greatly reduced in size.

Comment

Idiopathic myelofibrosis is a chronic myeloproliferative disorder in which marrow fibrosis and myeloid metaplasia occur secondary to a neoplastic, clonal, hematopoietic cell proliferation. Megakaryocytes have a crucial role in this, and in some cases there may be increased platelet production with little or no initial marrow fibrosis, leading to a false diagnosis of essential thrombocythemia. It is possible that some of the patients previously reported as having essential thrombocythemia and who developed CML had in fact initially had idiopathic myelofibrosis.

CML can present with thrombocytosis and a minimal leukocytosis and can be wrongly diagnosed as essential thrombocythemia. The presence of the Philadelphia chromosome should always be thoroughly sought in such a situation. The clinical relevance of the presence of a BCR/ABL transcript in a patient without a demonstrable Philadelphia chromosome as seen by FISH or karyotype analysis and without hematological evidence of CML is dubious. Certainly such patients should be carefully watched clinically and assessed with quantitative PCR since cryptic translocations can occur.

In our patient there was no cytogenetic or molecular evidence of CML 9 years before its development. It is unlikely that a small clone of undetected CML had been present initially since it did not develop during those 9 years. Although he received

CML = chronic myeloid leukemia

WBC = white blood cells
PCR = polymerase chain reaction

FISH = fluorescent in situ hybridization

analgrelide, which may increase myelofibrosis in essential thrombocythemia [5], he did not receive treatment with hydroxyurea or any potential neoplastic-inducing or incriminating agent. This suggests that the CML was a secondary event occurring many years after idiopathic myelofibrosis. As a secondary event, CML can also occur in other situations such as during acute myeloid leukemia, although in these cases it may have been caused by chemotherapy. Our patient, who did not have previous chemotherapy, would fit in with Dameshek's original suggestion that all the chronic myeloproliferative diseases are inter-related.

References

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