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Brief communication

A myeloproliferative disorder may hide another one

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ABSTRACT

Chronic myeloproliferative disorders (MPDs) are divided into Philadelphia-positive chronic myeloid leukemia (CML) and Philadelphia-negative disorders including polycythemia vera, essential thrombocythemia and idiopathic myelofibrosis (IMF). Concomitance of a CML and another MPD is a rare event. We report here the case of a patient presenting initially with IMF who developed a Philadelphia-positive CML 7 years later. At the time of CML diagnosis, two distinct clones were present, one with a 13q deletion and one with a t(9;22). We raise the problem of a CML developing on an initial IMF, or two MPDs occurring from a common or two different stem cells.

Chronic myeloproliferative disorders (MPDs) are divided into Philadelphia-positive chronic myeloid leukemia (CML) and Philadelphia-negative disorders including polycythemia vera, essential thrombocythemia and idiopathic myelofibrosis (IMF). Concomitance of a CML and another myeloproliferative disorder is a very rare event [1]. IMF is characterized by an increase in reticular fibers associated with a progressive obliteration of the bone marrow and an extramedullary hematopoiesis. Karyotype shows cytogenetic abnormalities in 50% of cases with about 20% of chromosome arm 13q deletion [2,3].

We report here the case of a patient presenting initially with IMF who developed a Philadelphia-positive CML 7 years later. Two distinct clones were concomitantly present, one with a 13q deletion and one with a t(9;22) translocation.

1. Case report

The patient, a 69-year-old man was diagnosed with IMF in 2001. Initial biological presentation was tricytopenia. No karyotype was done and no treatment was given. In November 2006, the white blood count (WBC) increased ($22 \times 10^9\,L^{-1}$) and a myelemia (30%) appeared. Hemoglobin level (134 g/L) and platelet count ($308 \times 10^9\,L^{-1}$) were normal. Physical examination revealed a slightly enlarged spleen. Bone marrow was normocellular with some dysmorphic megakaryocytes, basophilia (3%) and dacryocytes. Karyotype on peripheral blood showed a t(9;22)(q34;q11) as the sole abnormality in 18/24 metaphases (75%). MBCR–ABL transcript was detected by quantitative reverse transcription polymerase chain reaction in peripheral blood cells (ratio MBCR–ABL/ABL: 3.4%). CML was finally diagnosed and a treatment by imatinib mesylate (IM) 400 mg/day was started.

In July 2007, bone marrow was hypocellular with a persistent basophilia (2%) and dacryocytes. At this time, the level of MBCR–ABL transcript was moderate in the peripheral blood (MBCR–ABL/ABL: 0.25%), reflecting a good response to IM. Bone marrow karyotype did not show any Philadelphia chromosome but an interstitial deletion of chromosome arm 13q, del(13)(q12q21) in 19/20 metaphases (95%) (Fig. 1). The WBC was normal and blood smears showed dacryocytes and erythroblasts (6%). The hemoglobin level was low (104 g/L). V617F JAK2 mutation, which is positive in about 50% of IMF [4], was not detected. MPLW515L/K mutation, which is positive in 5 to 10% of IMF [5], was not tested.

Retrospective FISH analysis performed on the cytogenetic pellet of November 2006 using the ES BCR–ABL (Vysis, USA) and 13q14.3 Aquarius® (Cytocell, UK) probes detected two distinct clones with a t(9;22)(q34;q11) in 75% of nuclei and metaphases, and a 13q deletion in 11% of nuclei and in less than 5% of metaphases (Fig. 2). Neither nuclei nor metaphases expressed both abnormalities.

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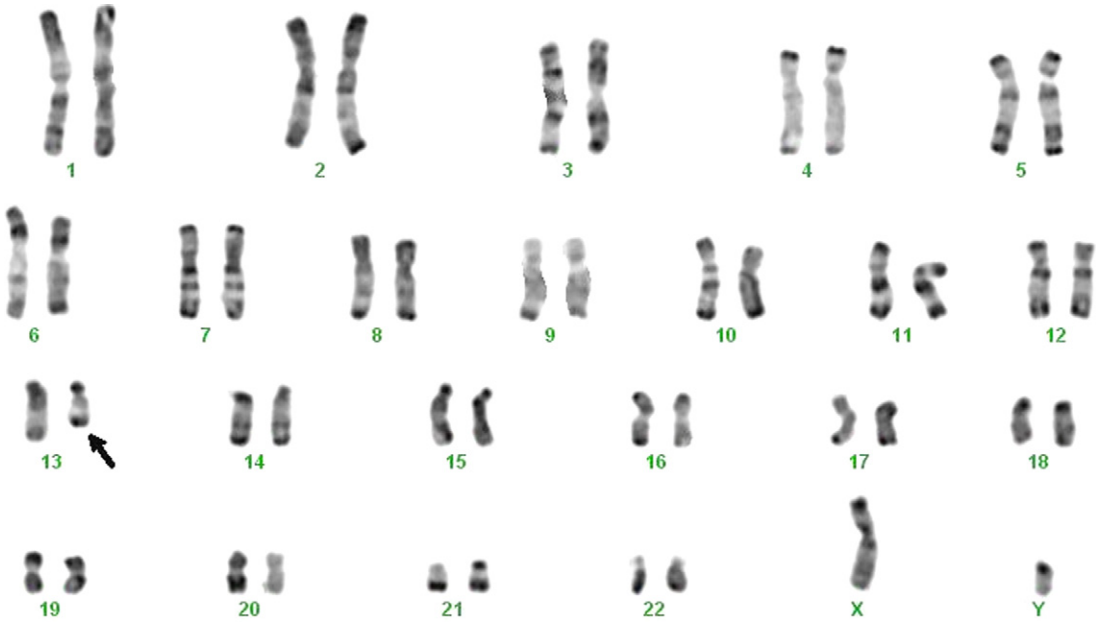

Fig. 1. Deletion of the chromosome 13q on bone marrow R-banded karyotype after imatinib mesylate treatment: del(13)(q12q21).

In January 2008, the MBCR–ABL transcript was still moderate (MBCR–ABL/ABL: 0.19%) but anemia and erythoblastosis persisted in the peripheral blood, with an increased platelet count (470 G/L). In July 2008, the patient still received IM 400 mg/day, bone marrow was hypocellular with megakaryocytic features of myelofibrosis. Karyotype showed 20/20 metaphases (100%) with the 13q deletion and the CML was in major molecular response (MBCR–ABL/ABL: 0.07%). In January 2009, the major molecular response persisted (MBCR–ABL/ABL: 0.05%).

2. Discussion

We report here the coexistence of two MPDs in a patient with initial IMF who developed CML 7 years later. To our knowledge, this is the first report of the coexistence of IMF and CML in a patient with evidence of two distinct cytogenetic clones. Some cases of coexisting MPDs have been previously reported where the MPD associated to CML was characterized by the JAK2 V617F mutation and not by cytogenetic abnormalities [6–9]. In other cases, the Philadelphia-negative MPD presented with cytogenetic abnormalities but was polycythemia vera [10,11] and not IMF.

Unlike some cases of transformation from MPD to CML after P32 treatment or chemotherapy treatment [12,13], our patient did not receive any treatment before CML diagnosis. Moreover, he had neither history of previous cancer nor known toxic exposure. Therefore, we hypothesize that the emergence of the CML is not therapy or toxic-related.

Imatinib mesylate was efficient on the CML, as proven by the disappearance of the Philadelphia-positive metaphases and the decrease of the MBCR–ABL transcript. In 5–10% of treated CML patients, cytogenetic abnormalities emerge in a Philadelphia-negative clone, but no 13q deletion has been reported in these cases [14,15]. Moreover, in our case, the 13q deletion clone was already present at the time of CML diagnosis. The increase of the clone with 13q deletion is probably related to the decrease of the Philadelphia clone under IM.

Three hypotheses may explain the occurrence of the CML on the IMF. The first one is the evolution of a pre-existing IMF into CML. In most of the previous observations, the MPD was positive for the JAK2 V617F mutation and it was proposed that the t(9;22) occurred in the JAK2 mutated clone [9,11]. Our case had distinct cytogenetic markers for the two pathologies and FISH analyses showed that t(9;22) did not occur in the clone with 13q deletion. A same observation was made in a case of simultaneous occurrence of CML and multiple myeloma. FISH analysis distinguished two malignant cell populations: plasma cells with 13q deletion and granulocytic cells with BCR–ABL fusion. As in our case, no cell was detected with both cytogenetic abnormalities [16]. An increase in the JAK2 mutated clone was reported in patients traited by IM [9]. These results would suggest the independence of the two clones, one with a JAK2 mutation and one Philadelphia positive. Indeed, in our patient, during IM treatment, the percentage of 13q deleted metaphases increased, and the clone with t(9;22) disappeared.

The progression of one clone concurrently with the decrease of the other one suggests the independent development of two different clones leading to two distinct disorders. The association between CML and another MPD has been reported, but Philadelphia-negative MPDs and CML are both rare disorders and a rapid statistical calculation about the probability of simultaneous occurrence of two independent MPDs is less than 1 case/10^9 or 10^{10} persons.

A third hypothesis would consider the probable existence of a common stem cell as the target of a first early event (mutation, epigenetic modulation...), leading to a chromosomal instability and favoring the development of two myeloproliferative disorders when a second event [either 13q deletion or t(9;22)] occurred. More studies are needed to confirm this clonal evolution.

In conclusion, our results suggest the need for searching for another MPD when a CML presents with atypical morphologic features (normocellular bone marrow, enlarged megakaryocytes) and/or persistence of anemia and basophilia in complete cytogenetic response to IM. This should not only be related to IM resistance, but the existence of another MPD must be considered and the JAK2 V617F mutation should be searched as well as cytogenetic abnormalities.