Presence of the bcr/abl rearrangement in a patient with chronic neutrophilic leukaemia

C Christopoulos, K Kotorris, V Mikraki, E Aneavis

Abstract

An 83 year old woman presented with a myeloproliferative disorder involving the myeloid and megakaryocytic lines, and characterised by mature neutrophil leucocytosis. There was a high/normal neutrophil alkaline phosphatase activity and absence of the Philadelphia chromosome, features compatible with a diagnosis of chronic neutrophilic leukaemia (CNL). Southern blot analysis of the patient's DNA revealed the presence of the bcr/abl rearrangement. Combined with a previous report of detection of Ph1 chromo-

some in long term bone marrow cultures in a patient with CNL, this finding suggests that the bcr/abl hybrid gene might occasionally result in a myeloproliferative disorder with a phenotype closely resembling that of CNL.


Keywords: chronic neutrophilic leukaemia, myeloproliferative disorders, chronic granulocytic leukaemia, bcr/abl rearrangement, Philadelphia chromosome.

Chronic neutrophilic leukaemia (CNL) is a rare myeloproliferative disorder, with about 40 cases reported in the literature since it was first described by Tsohoy in 1920.15 Seen mostly in the elderly, it is related to chronic granulocytic leukaemia (CGL) from which it is differentiated by the paucity of immature granulocytes in the peripheral blood, the increased neutrophil alkaline phosphatase activity and the absence of the Philadelphia (Ph') chromosome. Despite its mature phenotype, CNL seems to have a prognosis considerably worse than that of CGL.

In the few cases of CNL on which molecular cytogenetic studies have been done, the bcr/abl rearrangement has not been found. Here, we present a case of Ph’ negative, bcr/abl positive myeloproliferative syndrome with the phenotype of CNL, suggesting that this rare disorder might occasionally represent the expression of the same oncogene that is activated in CGL.

We propose that the criteria for diagnosis of CNL be redefined.

Case report

An 83 year old woman was admitted to hospital for investigation of leucocytosis discovered a few days prior to her admission when she had presented with one month’s history of progressive weakness, lassitude and weight loss. There was a history of mild hypertension and exertional dyspnoea of recent onset. The patient was not taking any medication. Physical examination revealed mild congestive cardiac failure but was otherwise unremarkable. Results of a full blood count were as follows: haemoglobin 12.9 g/dl; white cell count (WBC) 59.7 x 10^9/l with 93% neutrophils, 2% lymphocytes, 3% monocytes, 1% myelocytes, 1% metamyelocytes; platelet count 494 x 10^9/l. There was a right shift of the mature neutrophils with notable nuclear hypersegmentation. Occasional erythroblasts were also present in the blood film. The platelets showed notable morphological abnormalities including giant and hypogranular cells; numerous platelet clumps were present. The neutrophil alkaline phosphatase (NAP) score was 156 (normal range in our laboratory 70–160). The erythrocyte sedimentation rate was 56 mm/hour. Serum biochemical profile (normal ranges in brackets) was within normal limits apart from a raised urate concentration at 0.52 mmol/l (0.16–0.43) and lactic dehydrogenase activity at 355 IU/l (96–176). The serum vitamin B12 concentration was raised at 1233 ng/l (250–1100) with normal folate, iron and ferritin concentrations. A chest x ray film showed vascular congestion and a computed tomography scan of the abdomen was normal; there was no splenomegaly or hepatomegaly. Bone marrow aspiration and biopsy samples were hypercellular with noticeably hyperplastic granulopoiesis and a myeloid:erythroid ratio of 10:1. The predominant cells were myelocytes, while the percentage of blasts was not increased (<2%). Megakaryocytes were increased in number with active platelet production. Erythropoiesis was normal.

Methods

Chromosome analysis was performed using the RGH labelling technique. Twenty metaphases were analysed and one was karyotyped. There were no structural or numerical abnormalities in any of the metaphases analysed. The Ph’ chromosome was not detected. The bcr/abl rearrangement in haemopoietic cells aspirated from the patient’s bone marrow was detected by Southern blotting. High molecular weight DNA was digested with the BglII restriction enzyme and hybridised to a phl/bcr-3 specific DNA probe (Transprobe-1, Oncogene Science) according to standard procedures.4 Autoradiography revealed the presence of an extra band confirming the existence of bcr/abl translocation (fig 1).

Nine days after being admitted to hospital, the patient developed signs of an illio-femoral deep vein thrombosis of the left lower extremity, which was confirmed by Doppler ultrasound. There was good response to heparin treatment followed by oral anticoagulation. At the same time hydroxyurea was introduced at a dose of 1 g/day, resulting in a fall in the WBC from 60 x 10^9/l to 16 x 10^9/l and the platelet count from 575 x 10^9/l to 170 x 10^9/l after two weeks of treatment. This was associated with notable symptomatic improvement. A dose of hydroxyurea of 0.5 g/day was required to maintain the WBC at 10–20 x 10^9/l and the platelet count at 150–200 x 10^9/l. The patient died suddenly at home three months after her initial presentation. A postmortem examination was not done.

Discussion

The primary myeloproliferative nature of this patient’s illness was confirmed by the combination of a persistent rise in the neutrophil count in the absence of a cause of the leukaemoid reaction, a hyperplastic bone marrow myelopoiesis including the myeloid and megakaryocytic lines, raised serum B12, and urate concentration, a raised lactic dehydrogenase activity, and the presence of the bcr/abl rearrangement. Table 1 shows the main clinical, haematological and cytogenetic features of the case presented here against those of typical cases of CGL and CNL. The absence of splenomegaly, unusual in a myeloproliferative disorder, was thought to be because of either functional hyposplenism of old age5 or atrophy following splenic infarctions, which are a common manifestation of the thrombotic tendency associated with myeloproliferative disorders. The cytogenetic abnormality is the hallmark of CGL but this diagnosis is incompatible with the paucity of immature granulocytes in the peripheral

Figure 1 Detection of the bcr/abl rearrangement by Southern blotting. Standard control bands are present at 4.8, 2.3 and 1.1 kilobases. Arrows indicate rearranged bands. P = patient DNA; NC = negative control; PC = positive control.
血小板，原淋巴细胞和单核细胞计数在骨髓和血液中都有高/正常水平。慢性移位性白血病（Chronic myelogenous leukemia）在分子水平，是慢性粒细胞白血病的等位基因可能在 AFP，一个 95% 的病例中检测到。在这些情况下，需要对 AFP 的检测。3

**Case report**

一个 44 岁的非洲男子，他有间歇性腰痛和血尿。他被诊断为慢性移位性白血病。没有需要的药物。研究显示了肾细胞癌的 MRI 扫描在左侧肾脏，肿瘤直径为 3.6 cm。这可能包括一个软组织。一个肾切开术是在和病人被送回家后七天。他继续 12 个月后做了手术。5

**Pathological findings**

显微镜下，肾内含有一块大而圆的肿瘤，3.6 cm。在肿瘤的外层，肾皮质，带有黄色的切面，和与肾盂相连。肿瘤的剩余组织是显微镜下正常。五名代表性的样本的肿瘤被取做显微镜下检查。显微镜下，所有部分都显示了肿瘤是编织型的。