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

C Christopoulos, K Kottorís, V Mikraki, E Anevlavis

Abstract
An 83 year old woman presented with a myeloproliferative disorder involving the myeloid and megakaryocytic lines, and characterised by mature neutrophil leukocytosis. 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. (J Clin Pathol 1996;49:1013–1015)

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 Tuohey in 1920.1-3 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 (Ph1) 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 Ph1 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 10⁹/l with 93% neutrophils, 2% lymphocytes, 3% monocytes, 1% myelocytes, 1% metamyelocytes; platelet count 494 x 10⁹/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 335 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 RHG labelling technique. Twenty metaphases were analysed and one was karyotyped. There were no structural or numerical abnormalities in any of the metaphases analysed. The Ph1 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 BgIII restriction enzyme and hybridised to a phl/bcr-3 specific DNA probe (Transprobe-1, Oncogene Science) according to standard procedures. 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 ileo-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 10⁹/l to 16 x 10⁹/l and the platelet count from 575 x 10⁹/l to 170 x 10⁹/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 10⁹/l and the platelet count at 150–200 x 10⁹/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 concentrations, a raised lactate 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 age4 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
Table 1 Characteristic clinical, haematological and cyto genetic features of CGL, CNL and patient DM

<table>
<thead>
<tr>
<th></th>
<th>CGL</th>
<th>CNL</th>
<th>Patient DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Splenomegaly</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Immature</td>
<td>Frequent</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>granulocytes in</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>peripheral blood</td>
<td>Low</td>
<td>High</td>
<td>High/normal</td>
</tr>
<tr>
<td>NAP</td>
<td>Present</td>
<td>Absent*</td>
<td>Absent</td>
</tr>
<tr>
<td>Ph' chromosome</td>
<td>85%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>bcr/abl hybrid gene</td>
<td>Present</td>
<td>Absent</td>
<td>Present</td>
</tr>
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*There is only one report of Ph' positive CNL in the English literature.5

blood, the normal myeloblast and promyelo-
cyte numbers in the bone marrow and the high/normal NAP score. The phenotype of this
myeloproliferative disorder combined with the
absence of Ph' chromosome would, in the pre-
molecular era, be sufficient for a diagnosis of
CNL. A Medline search of the English
literature identified only one case of CNL in
which the Ph' chromosome was detected in
long term culture.5 The bcr/abl rearrangement
has been consistently absent in the few cases
in which relevant studies have been done but the
need for more data has also been stressed.1 The
presence of the bcr/abl rearrangement in the
case reported here suggests that the repertoire
of the phenotypic expression of the hybrid bcr/
abl gene might include a disorder closely
resembling CNL. This calls for redefinition of
the diagnostic criteria for CNL to include the
absence of bcr/abl, as a projection of the gener-
ally accepted requirement for absence of a Ph'
chromosome. Even so, cases like the one
presented here will remain difficult to classify,
reflecting the presence of a continuum within
the myeloproliferative group of chronic myel-
oid leukemias.


Myxoid renal cell carcinoma: histological,
imunocytochemical and ultrastructural study

H A Birch, J M Glass, J Vale, M M Walker

Abstract
Renal cell carcinomas show a variety of
histological features. A case of a renal
tumour arising in a 44 year old African
man is reported. The tumour was com-
posed of a cobweb-like pattern of narrow
anastomising tubules lined by cuboidal
cells separated by a hypocellular myxoid
stroma. Immunohistochemical stains
were consistent with a renal cell origin.
The differential diagnosis in these cases
includes sarcoma. (J Clin Pathol 1996;49:
1015-1017)

Keywords: renal cell carcinoma, histological variants.

Renal cell carcinomas exhibit a wide variety of
cytological and architectural appearances. Chromophilic tumours (of eosinophilic or
basophilic type) usually exhibit a tubulo-
papillary growth pattern with cells separated by
a small volume of fibrovascular stroma.1 Here,
we report an unusual chromophilic renal cell
carcinoma with a microtubular growth pattern
and abundant myxoid stroma.

Case report
A 44 year old African man presented with
intermittent loin pain and haematuria. He had
been hypertensive for 10 years and had a
history of childhood schistosomiasis. He was a
non-smoker with no risk factors for renal
disease. There was a family history of hyper-
tension. A renal ultrasound scan revealed a
mass in the left kidney, which was confirmed
on computed tomography scanning. A radical
nenphrectomy was performed and the patient
was discharged home seven days later. He
remains well 12 months after the operation.

Pathological findings
Macroscopically, the kidney contained a well
defined rounded tumour, 3.6 cm in diameter,
within the cortex of the upper pole, confined
within the renal capsule and with a soft yellow
cut surface with areas of haemorrhage. The
remaining renal tissue was macroscopically
normal. Five representative samples of the
tumour were taken for histological examina-
tion. Microscopically, all sections showed that
the tumour was composed of a cobweb-like

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