Large granular lymphocyte leukaemia

development of the NK cells has not been elucidated, it has been suggested that these cells could be precursors of those with the CD3^+CD16^-CD56^- phenotype, which are the main NK cells in normal individuals. Increased counts of NK CD3^+CD16^-CD56^- cells have been reported in a group of patients after bone marrow transplant or treatment with interleukin 2,4 suggesting that these procedures could mobilise these hypothetical precursor cells towards the circulating blood.

The phenotypes of tumour cells have often permitted the prediction of unknown links in T and B lymphoid differentiation. We believe that the phenotype in NK cell leukaemias could also provide clues for elucidating the ontogeny of NK cells. One antigenic characteristic common to all the NK/LGL leukaemias described in published reports, including our patient, is the lack of expression of CD7. This is a surface antigen expressed by normal T and NK cells. Some models postulate that in the differentiation of the NK cells, the expression of CD7 might be a very early occurrence,2 16 as is the case in T cell differentiation. Less than 2% of the NK cells in the peripheral blood of normal subjects have the CD7^-CD56^ phenotype, supporting the probability that these are early precursors of CD7^-CD56^- NK cells. However, the absence of CD7 in the leukemic NK cells might indicate that this marker is expressed in NK cells following the expression of other markers, such as CD2 or CD56, which are expressed in all the cases of NK/LGL leukaemia reported to date.

HLA-DR is not expressed by the majority of normal NK cells, only by activated ones, so it should not be surprising that this feature is absent in our patient. The curious fact is that our patient is the only one who did not express HLA-DR among all the cases of NK/LGL leukaemias studied. In patients treated with interleukin 2, a small but significant (2–3%) proportion of peripheral blood lymphocytes cells with the CD3^-CD7^-CD8^-CD16^-CD56^- HLA-DR^- phenotype can be measured,6 showing that this cell type exists in the peripheral blood, at least when given certain stimuli. The neoplastic cells observed in our patient could represent a leukaemic counterpart of this hypothetical NK cell precursor.

The present case had clinical and haematological features similar to typical Japanese NK/LGL leukaemia, which suggests it is the same entity presenting in a European patient. We conclude that the rare occurrence of NK/LGL leukaemia and the peculiar immunophenotype of the blast cells, which as far as we know is the first to be described, lends special interest to the present case.


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

C Christopoulos, K Kottorís, V Mikraki, E Aneviáşi

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-


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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 myeloprolif-
erative disorder with a phenotype closely
resembling that of CNL.


Keywords: chronic neutrophilic leukaemia, myeloprolif-
erative 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 alka-
line 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 pheno-
type 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 hospi-
tal for investigation of leucocytosis discovered a
days prior to her admission when she had
presented with one month’s history of progres-
sive 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. Re-
sults of a full blood count were as follows: haem-
moglobin 12.9 g/dl; white cell count (WBC)
59.7 × 10^9/l with 93% neutrophils, 2% lympho-
cytes, 3% monocytes, 1% myelocytes, 1%
metamyelocytes; platelet count 494 × 10^9/l.
There was a right shift of the mature
neutrophils with notable nuclear hypersegmen-
tation. Occasional erythroblasts were also
present in the blood film. The platelets showed
notable morphological abnormalities including
large and hypogranular cells; numerous plate-
let 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 vita-
min B12 concentration was raised at 1233 ng/l
(250–1100) with normal folate, iron and ferr-
tin concentrations. A chest x ray film showed
vascular congestion and a computed tomogra-
phy scan of the abdomen was normal; there was
no splenomegaly or hepatomegaly. Bone mar-
row aspiration and biopsy samples were hyper-
cellular with noticeably hyperplastic granulo-
poiesis 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. Eryth-
ropoiesis was normal.

Methods
Chromosome analysis was performed using the
RHH 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 BglII restriction
enzymes and hybridised to a phl/bcr-3 specific
DNA probe (Transprobe-1, Oncogene Sci-
ence) 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 ilio-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 × 10^9/l to
16 × 10^9/l and the platelet count from 575 × 10^9/l
to 170 × 10^9/l after two weeks of treatment. This
was associated with notable symptomatic im-
provement. A dose of hydroxyurea of 0.5 g/day
was required to maintain the WBC at 10–20 ×
10^9/l and the platelet count at 150–200 × 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 combina-
tion of a persistent rise in the neutrophil count
in the absence of a cause of the leukaemoid
reaction, a hyperplastic bone marrow myelo-
poiesis including the myeloid and megakaryo-
cytic lines, raised serum B12, and urate concen-
trations, a raised lactic dehydrogenase activity
and the presence of the bcr/abl rearrangement.
Table 1 shows the main clinical, haematologi-
cal and cytogenetic features of the case
presented here against those of typical cases of
CGL and CNL. The absence of splenomegaly,
unsual in a myeloproliferative disorder, was
thought to be because of either functional
hyposplenism of old age4 or atrophy following
spenic infarctions, which are a common mani-
festation of the thrombotic tendency associated
with myeloproliferative disorders. The cyto-
ge netic abnormality is the hallmark of CGL but
this diagnosis is incompatible with the paucity
of immature granulocytes in the peripheral

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Figure 1 Detection of the bcr/abl rearrangement by
Southern blotting. Standard
closeup bands present at
4.8, 2.3 and 1.1 kilobases.
Arrows indicate rearranged
bands. P = patient DNA;
NC = negative control; PC =
positive control.
Myxoid renal cell carcinoma: histological, immunocytochemical 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 composed of a cobweb-like pattern of narrow anastomosing 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.

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 hypertension. A renal ultrasound scan revealed a mass in the left kidney, which was confirmed on computed tomography scanning. A radical nephrectomy 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 examination. Microscopically, all sections showed that the tumour was composed of a cobweb-like

Table 1  Characteristic clinical, haematological and cytogenetic 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 granulocytes in peripheral blood</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>NAP</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Ph' chromosome</td>
<td>Low</td>
<td>High</td>
<td>High/normal</td>
</tr>
<tr>
<td>Ph' chromosome</td>
<td>Present</td>
<td>Absent*</td>
<td>Absent</td>
</tr>
<tr>
<td>Bcr/abl hybrid gene</td>
<td>Present</td>
<td>Absent</td>
<td>Present</td>
</tr>
</tbody>
</table>

*There is only one report of Ph' positive CNL in the English literature.3

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