CASE REPORT

e19a2 BCR–ABL fusion transcript in typical chronic myeloid leukaemia: a report of two cases

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This report describes two patients with chronic myeloid leukaemia (CML): one of them developed accelerated phase CML and died 8 years after diagnosis and the other is at the chronic phase. Sequence analysis of reverse transcription-polymerase chain reaction products showed the presence of BCR–ABL fusion transcript e19a2. This finding suggests that CML carrying μ-BCR breakpoint may exhibit a clinical course similar to typical CML.

Most cases of chronic myeloid leukaemia (CML) are characterised by a BCR–ABL fusion protein originating from the t(9;22) chromosomal translocation, which is a molecular marker of the disease. The exact breakpoint of the translocation and the molecular weight of the resulting fusion gene protein vary. In most cases, the breakpoint on chromosome 22, falling in the so-called major breakpoint cluster region between exons 13 and 14 of the *BCR* gene (M-bcr), leads to a hybrid BCR–ABL mRNA with a b2a2 or b3a2 junction, which encodes a p210 fusion protein associated with the underlying mechanism, in the chronic phase of CML. Cases of CML with breakpoints in other regions are seen in other regions, namely minor (m-bcr) and micro (μ-bcr) bcr region, but to date, these cases are few in number and are associated with peculiar phenotypes. The m-bcr breakpoint, which is associated with acute lymphoblastic leukaemia, and rarely with acute myeloid leukaemia, connects exon 1 of BCR with ABL, producing a 190-kDa protein. The μ-bcr breakpoint connects exon 19 of BCR with ABL (exon 2 of which is the joining point in all three cases), giving rise to the e19a2 transcript corresponding to the p230 fusion protein, which has been associated with a mild CML phenotype.[1 2] Pane *et al*[2] proposed classifying these later cases as neutrophilic CML, a rare disease characterised by moderate and persistent neutrophilia without precursors in the peripheral smear, absent or normal splenomegaly and a benign clinical course, with a lower white cell count with minimal basophile, a milder anaemia.

So far, the e19a2 transcript has been observed in neutrophilic CML (n = 5), CML in chronic phase (n = 7), CML rapidly evolving to the blastic phase (n = 4) and acute myeloid leukaemia (n = 2).[1–6]

We describe two patients with CML with the e19a2 junction. Written informed consent was obtained from both the patients.

One of the patients is a 38-year-old man diagnosed in 1997 with classic CML and treated with hydroxyurea. In January 2004, his peripheral blood findings were haemoglobin 6.6 g/dl, mean corpuscular volume 112 fl, white cell count 3.6×10^9/l, with differential counts neutrophils 44%, lymphocytes 33%, monocytes 0%, eosinophils 05%, basophils 07%, myeloblasts 1%, promyelocytes 1%, myelocytes 2%, metamyelocytes 5% and platelets 736×10^9/l. In February 2004, his basophile count in peripheral blood increased to 14% and bone marrow smear examination showed 16% blast cells, indicative of the accelerated phase of CML. On examination, it was observed that he had mild anaemia and no haemorrhage, the liver was palpable 6 cm below the coastal margin and splenomegaly was absent, but he had fever, night sweats and weight loss in 5 weeks duration. He had generalised lymph node enlargement and the largest lymph node in his left axilla was palpable. The patient was started on imatinib mesylate treatment, as CML was at the accelerated phase. He died in May 2004.

The second patient was a 19-year-old man having high white cell count, chronic anaemia and hepatosplenomegaly. He first presented in February 2004, with low-grade fever for the past 5 months, breathlessness, fatigue, hepatosplenomegaly, chronic anaemia and priaprism. The peripheral blood findings were haemoglobin 11.4 g/dl, MCV 62 fl, white cell count 587×10^9/l, with differential counts neutrophils 40%, lymphocytes 0%, monocytes 0%, eosinophils 05%, basophils 06%, myeloblasts 1%, myelocytes 27%, metamyelocytes 21% and platelets 541×10^9/l. His bone marrow aspirate examination was hypercellular, with bone smear showing 4% blasts. The patient was started on hyroxyurea treatment 2000 mg/day and later 1500 mg/day as a patient with typical CML at

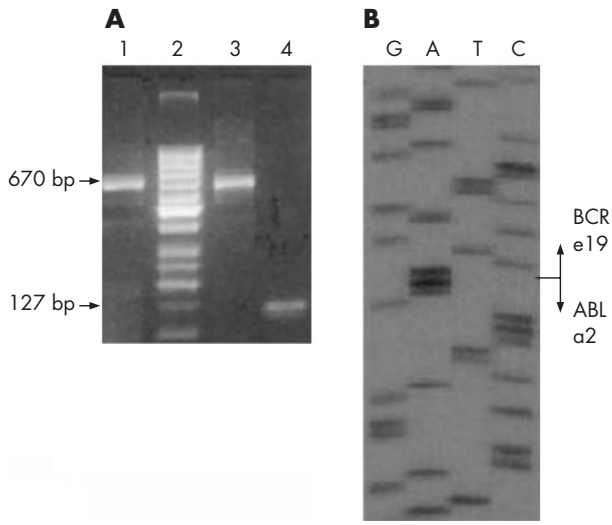

Figure 1 (A) Reverse transcription-polymerase chain reaction (RT-PCR) product of the *BCR–ABL* fusion gene (ethidium bromide-stained 3% agarose gel); lanes 1 and 3, e19a2 transcript from the bone marrow cells of the two patients using BcrF and AblR primers; lane 2, molecular weight marker; lane 4, b3a2 transcript from the K562 cell line using the same primers. (B) Sequence analysis of the RT-PCR product.

Abbreviation: CML, chronic myeloid leukaemia

the chronic phase as per institutional protocol. He is well to date.

In both cases, cytogenetic analysis could not be carried out owing to the absence of mitosis.

Reverse transcription-polymerase chain reaction analysis of the fusion transcript using primers specific for the major breakpoint (BcrF: TCCACTCAGCCACTGGATTTAA and AblR: TGGGTCCAGCGAGAAGGTT) failed to show bands corresponding to the b3a2 transcript. However, a band of about 670 bp was seen (fig 1A) with the M-bcr primers, suggesting the presence of a downstream BCR breakpoint consistent with an e19a2 transcript. This was confirmed by direct sequence analysis of the amplified products (fig 1B).

Recent experimental findings on in vivo leukaemogenic activity of p230 protein compared with the other BCR–ABL forms are not consistent. Li *et al*[7] proposed that the e19a2 rearrangement is indicative of good prognosis, and others found that p230 induced a myeloproliferative disease with much longer latency than that induced by p185 and p210 BCR–ABL,[8 9] and thrombocytosis.[9] Neutrophilic CML is characterised by a more benign course compared with typical CML, with lower white cell count with minimal basophile, a milder anaemia and less prominent splenomegaly.[2] By contrast, our first patient had typical CML at the accelerated phase, with increased basophiles in the blood, increased blast cells in bone marrow and lower white cell counts. The second patient had typical CML at the chronic phase with marked basophiles, hepatosplenomegaly and high white cell counts. From the two cases of typical CML in the accelerated and chronic phase with e19a2 reported here, we opine that there is more evidence in support of the recent viewpoint that perhaps this new transcript is not associated with a particular type of myeloproliferative syndrome.

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