CASE REPORT

The 8p12 myeloproliferative syndrome

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ABSTRACT

The occurrence of a myeloproliferative disorder in association with an aggressive lymphoproliferative disorder is a distinctly unusual phenomenon. We report a case of concurrent leukaemia-lymphoma syndrome characterized by a BCR/ABL-negative myeloproliferative disease, eosinophilia and a lymphoma. The bone marrow chromosome analysis showed the karyotype 46, XY, t(8;9) (q12; p33), which indicated presence of *FGFR1* gene translocations. 8p12 myeloproliferative syndrome (EMS) / stem cell leukaemia-lymphoma syndrome (SCLL) belongs to the tyrosine kinase fusion genes chronic myeloproliferative diseases. The patient was managed conservatively with hydroxyurea, allopurinol and blood component therapy. The patient eventually died of intracerebral haemorrhage due to severe thrombocytopaenia.

Based on our experience the overlap in the clinical presentation of this disease with lymphomas, can lead to a delay in diagnosis of EMS/SCLL. Given the aggressive nature of this disease, an accurate clinical and molecular diagnosis of this entity has become increasingly important.

Key words: Eightp myeloproliferative syndrome, stem cell leukaemia lymphoma syndrome

INTRODUCTION

The 8p12 myeloproliferative syndrome (EMS)/stem cell leukaemia/lymphoma (SCLL) is a relatively rare condition characterised in its typical form by the occurrence, either simultaneously or sequentially, of a bcr/abl-negative myeloproliferative disorder, eosinophilia and a lymphoma, usually a precursor T-lymphoblastic lymphoma. The disease is aggressive and rapidly transforms to acute leukaemia, usually of myeloid phenotype in a median of 6 months.[1]

When EMS/SCLL was first identified as a syndrome in the early-mid 1990s, cases were included which met both cytogenetic and clinical criteria, namely a translocation involving 8p11-12 and usually 13q11-12 as well as an atypical myeloproliferative syndrome diagnosed simultaneously with or in close temporal relationship to an immature T-cell lymphoma. Except for occasional patients who underwent bone marrow or peripheral stem cell transplantation, these patients typically developed and succumbed to AML. In more recent years, the designation of EMS has been applied to any case in which a translocation involving 8p11-12 (*FGFR1*) has been demonstrated. At least eight partner genes in the FGFR1 translocation have been identified, and the clinical manifestations are nearly as varied as the number of reported cases.[2-10] The t(8;9) (p12;q33) is a variant of the translocation t(8;13) (p12;q12).[1]

This disease is aggressive and survival is very short (median survival 12 months). Cytogenetic analysis remains the mainstay of diagnosis and currently, only allogeneic stem cell transplantation appears to be effective in eradicating or suppressing the malignant clone.

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CASE REPORT

A 49-year-old man presented with generalised lymphadenopathy, difficulty in breathing due to cervical nodal enlargement over the prior 5 months. He also reported several systemic symptoms including malaise, drenching night sweat and generalised arthralgia.

At admission, enlarged lymph nodes that were fixed, discrete and elastic were palpated in neck, axillary and inguinal areas. Liver and spleen were not palpable. Other physical findings were unremarkable.

CT scan demonstrated multiple bilateral nodes in the parotid, submandibular, supraclavicular, cervical and deep

to the sternocleidomastoid at the levels of the suprahyoid, intrahyoid and cricoid cartilage. No involvement of the mediastinum was noted.

A complete blood count revealed a hemoglobin level 13g/L, a platelet count 90 × 10^9/L, a white cell count 59 × 10^9/L with 6% promyelocytes, 2% myelocytes, 4% metamyelocytes, 5% bands, 9% neutrophils, 40% eosinopils, 4% basophila, 18% monocytes and 10% lymphocytes [Figure 1a]. The liver biochemistry profiles and renal function test were normal.

Bone marrow aspiration done showed a hypercellular (~90%) marrow with active myeloid lineage and moderate eosinophilia and monocytosis. There was no marked erythroid dysplasia and blasts were not increased [Figure 1b]. Meanwhile, a biopsy of a submental lymph node done was suggestive of an angioimmunoblastic lymphoma.

The differentials on admission included chronic myelomonocytic leukaemia, hypereosinophilic syndrome and leukaemia-lymphoma syndrome.

He was managed conservatively and commenced on prednisolone, hydroxyurea. Patient's clinical condition improved with complete regression of lymph nodes and normalisation of blood picture.

In Hamburg University, Germany, cytogenetic analysis of the bone marrow aspirate done showed the following karyotype: 46, XY, t(8;9)(p12;q33), BCR- ABL rearrangement was not detected by polymerase chain reaction. A definitive diagnosis of EMS was then made.

He subsequently had a relapse and developed resistance to hydroxyurea with increasing WBC count, anaemia and thrombocytopaenia [Table 1], he died of intracerebral haemorrhage secondary to severe thrombocytopaenia 8 months after presentation before he could have a stem cell transplant.

DISCUSSION

Concurrent myeloid and lymphoid malignancies are quite uncommon. The case detailed above exhibits many features typical of the EMS/SCLL, including male sex; constitutional symptoms at presentation; an aggressive lymphoma with generalised lymphadenopathy which spares the mediastinum; peripheral blood leukocytosis and eosinophilia; bone marrow myeloid hyperplasia; development of acute leukaemia which is resistant to standard chemotherapy; and a chromosome karyotype with the defining 8p11-12 translocation.[11] The characteristic chromosomal translocation always involves the fibroblast growth factor receptor 1 (*FGFR1*) gene at chromosome 8p11-12.[2]

Normal FGFR1 [Figure 2] is a trans-plasma membrane protein with an extracellular ligand-binding domain, a transmembrane domain and a cytoplasmic tyrosine kinase domain. FGFR1 and its relatives FGFRs 2-4 play important roles in early development, in conjunction with their ligands, the fibroblast growth factors (FGFs), of which there are currently more than 20 members.[12] FGFRs may also impact on haemopoiesis, although their role in this context has not been clearly defined.[13]

In their inactive state, receptors such as FGFR1 are thought to exist as monomers in the plasma membrane. Binding of FGF ligands induces dimerization, which juxtaposes the two catalytic domains, inducing a conformational change which partially activates the

Table 1: Serial blood count

	2/4/10	19/4/10	20/5/10	22/6/10	25/7/10	2/8/10	22/10/10	8/11/10
Hb	13	13	11.5	10.7	12.2	11.7	8.5	6.5
PCV	39	39	39	36.1	36.7	38.1	26	19.4
WBC	59	80.3	23.3	21.1	9.6	4.7	52.4	95.6
Platelet	90	134	106	105	117	177	41	19

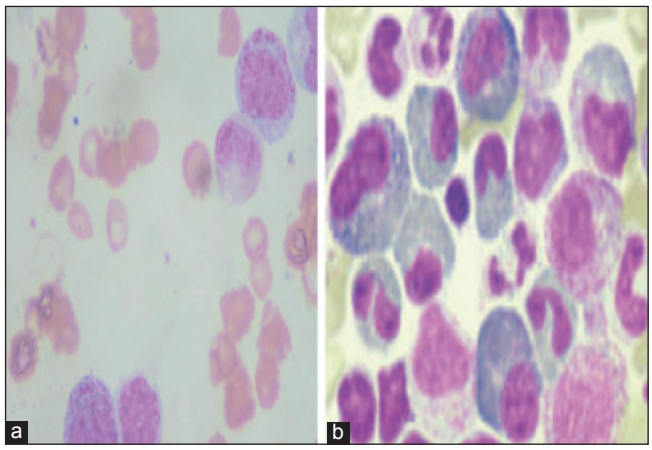

Figure 1: Peripheral Blood film and Bone Marrow Aspirate

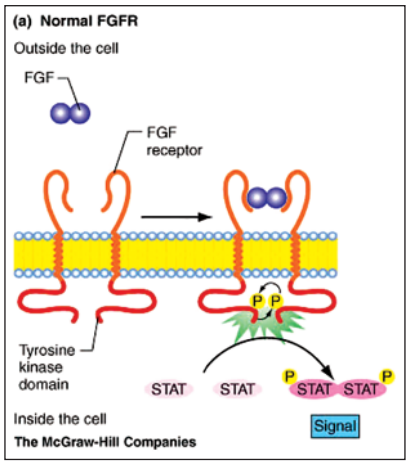

Figure 2: Diagram of normal FGFR

enzymatic activity. This leads to transphosphorylation of a key tyrosine residue in the activation loop resulting in an increase in enzymatic activity, phosphorylation of additional tyrosines and subsequently phosphorylation and/or recruitment of target substrates.[12,14] Normal FGFRs activate multiple signalling pathways including those involving Ras/MAPK, P13K, PLCÁ and STAT proteins. The t(8;9)(p12;q33) distrupts exon 8 of the FGFR1 gene and fuses leucine zippers domain of the CEP110 gene with the cytoplasmic tyrosine kinase domain of FGFR1.[1] Oligomerisation of the fusion protein occurs, which mimics the initial stage of normal tyrosine kinase activation, with subsequent activation of downstream signal transduction pathways, culminating in neoplastic cell transformation. All of the fusion transcripts studied thus far has been shown to have constitutive, ligand-independent tyrosine kinase activity. These pathways and the fusion proteins are attractive targets for targeted signal transduction therapy.[1,11]

At least 8 partner genes in the FGFR1 translocation have been identified [Table 2], and the clinical manifestations are nearly as varied as the number of reported cases.[2-10] For example, two patients with a t(6;8) and a FOP-FGFR1 fusion were diagnosed initially as having polycythemia vera.[4] Thrombocytosis and monocytosis have been described relatively frequently in patients with a t(8;9), and thus the disease with this translocation resembles CMML but without major dysplastic signs in either lineage.[2,15] The incidence of T-NHL appears to be considerably higher in cases that present with a t(8;13) compared to patients with variant translocations. For example, in a recent survey 13/16 patients with a t(8;13) had T-NHL compared to 3/11 patients with a t(6;8) or t(8;9).[13] Cytogenetic analysis remains an important front-line test in suspected cases.

EMS has features that are similar to other well defined MPDs like CML and CMML as seen in the above case. Also in addition it is frequently associated with T-cell and less commonly B cell NHL, there is often a difficulty of diagnosis as illustrated in the present case.

At presentation, generalized lymphadenopathies led to the diagnosis of a lymphoma. However, the peripheral blood picture was similar to CMML; given the dearth of facilities for cytogenetic analysis in our environment this resulted in a delay in diagnosis of this patient.

Another challenge we faced was in the treatment options, in view of the simultaneous expression of myeloid and lymphoid lineage features, consideration of chemotherapeutic regimens is similar to that of bi-phenotypic leukaemia. As a result, we chose treatment that was based on cytoreduction. Steroids were included in the induction phase and remission was achieved for both leukaemia and lymphoma. We believe allogeneic stem cell transplantation is an effective, although risky treatment option and an accurate and timely diagnosis of this condition will leave room for this option.

Table 2: FGFR1 gene fusion partners

Year	FGFR1 gene fusion partner	Location	References
1998	ZNF198	13q11-12	Xiao S *et al.* [2]
1999	FOP/FGFR1OP	6q27	Popovici C *et al.*[4]
2000	CEP110	9q33	Guasch G *et al.*[7]
2001	BCR	22q11	Demiroglu A *et al.*[8]; Fioretos T *et al.* [5]
2003	HERV-K	19q13	Guasch G *et al.*[9]
2004	FGFR1OP2	12p11	Grand EK *et al.*[10]
2005	TIF1	7q34	Belloni E *et al.*[6]
2005	MYO18A	17q23	Walz C *et al.*[3]

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