8p11 myeloproliferative syndrome: diagnostic challenges and pitfalls

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Summary

8p11 myeloproliferative syndrome (EMS) is a very rare clinicopathological entity which is characterized by the appearance of a myeloproliferative neoplasm in the bone marrow, peripheral lymphadenopathy, usually caused by T or B lymphoblastic lymphoma/leukemia, and a reciprocal translocation involving chromosome 8p11. EMS has a highly aggressive clinical course, usually evolving to an acute myeloid leukemia (AML) refractory to conventional chemotherapy [1]. We recently had the chance to come across a 22-year-old man who presented with epistaxis which led to a CBC analysis showing an elevated hemoglobin (17.7g/dl, range 12-16g/dl), thrombocytopenia (98x10^9/l, range 150-450x10^9/l) and leukocytosis (57x10^9/l, range 4-10x10^9/l). The white cell differentials revealed eosinophilia of 9%, with a leukoerythroblastic picture and left shift (neutrophils 51%, bands 16%, metamyelocytes 3%, myelocytes 1%, promyelocytes 3%, lymphocytes 7%, monocytes 9%). A biochemistry profile showed elevated LDH 657 IU/l (range 155-
214 IU/l) and uric acid 559 µmol/l (range 143-339 IU/l). Bone marrow aspirate and biopsy revealed the presence of a MPN. Allele specific PCR and RT-PCR did not identify a JAK2 V617F mutation or aBCR-ABL p210 rearrangement, respectively. Cytogenetic analysis revealed t(8;13)(p11q12) (Figure 1a), and a ZMYM2-FGFR1 in-frame fusion was confirmed at the molecular level (Figure 2). Immediately after establishing diagnosis of MPN, cervical and inguinal lymphadenopathy was developed. Computed tomography scans of the chest, abdomen and pelvis revealed mediastinal lymphadenopathy (3.2x3.6x5.2cm) as well as intraabdominal and retroperitoneal enlarged lymph nodes (hepatic and splenic hilar, celiac, mesenteric) measuring up to 3.7cm and significant splenomegaly (18.0cm). A cervical lymph node biopsy was performed and histopathologic examination confirmed the diagnosis of a T cell lymphoblastic lymphoma with the following immunophenotypic profile: TdT+, CD3+, CD5+/-, CD4+, CD7+, CD43+, bcl-2+, CD8-, CD34-, CD117-, PAX-5-, CD20-, CD15-, CD30-; Ki 67 positivity was detected in 60% of tumor cells. Central nervous system infiltration was excluded by flow cytometry of the cerebrospinal fluid. The diagnosis of EMS was established. The patient was treated with 4 cycles of HyperCVAD chemotherapy, with complete morphological and

![Figure 1a. t(8;13)(p11q12).](image1)

![Figure 1b. t(8;13) accompanied by complex numerical and structural aberrations. Arrows show basic structural aberration of t(8;13) (p11;q12) among other structural and numerical aberrations which arose during disease evolution.](image2)
cytogenetic remission and resolution of lymphadenopathy. During the preparation for allo-SCT from his HLA matched sister, 4 weeks after completion of chemotherapy, he developed peripheral blood monocytosis and eosinophilia, along with a left shift, but without blasts. A bone marrow aspiration was performed confirming the recurrence of the MPN. Repeated cytogenetic analysis on this bone marrow sample showed a pathologic karyotype with evolution: 12 of 20 cells had an isolated t(8;13), and 8 of 20 contained hyperdiploidy with t(8;13) accompanied by complex numerical and structural aberrations (Figure 1b). Because of generalized lymphadenopathy recurrence, lymph node biopsy was repeated confirming the previous diagnosis of T cell lymphoblastic lymphoma. The patient underwent allo-SCT and achieved complete remission.

Discussion

We described a patient with EMS. This is a very rare entity that occurs within a wide age range [3,4] with median peak age in the early 40’s [1]. The disease has a slight male predominance. Approximately one fifth of the patients are asymptomatic, with the disease discovered after performing routine blood analysis for unrelated reasons. The remaining present with constitutional symptoms, such as fatigue, weight loss, night sweats and/or fever. On physical examination, lymphadenopathy is noted in two thirds of the patients, with occasional localized lymph node enlargement, [5] and, rarely, mediastinal lymphadenopathy [6,7]. Splenomegaly is a common feature (up to 60%), with hepatomegaly seen in less than one third of the cases, usually in combination with an enlarged spleen. Extranodal sites of disease are unusual findings [1,2]. Peripheral blood leukocytosis is a common finding, with increased absolute number of eosinophils and monocytes. The absolute basophil count is normal, except in cases with t (8;22) when it is commonly elevated [1]. Circulating blasts are present in half of these patients. More than 50% of the reported cases presented with normal hemoglobin levels, while the remainder showed either increased hemoglobin with an increased red blood cell mass, or a normo-

Figure 2. The protein structures of normal ZMYM2, normal FGFR1 and chimeric ZMYM2-FGFR1 are depicted. The domain structures were taken from the UniprotKB/Swiss-Prot Database. Numbers above the structures indicate the aminoacid position of the breakpoint. The new fusion transcript results from an in-frame fusion between ZMYM2 coding exon 14 and FGFR1 exon 9. The kinase domain of FGFR1 is retained in the chimeric protein. The Sanger sequencing trace from the described patient sample is shown in the lower panel.
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cytic anemia. Mild to moderate thrombocytopenia is common [1]. Bone marrow aspirate and biopsy findings show hypercellularity, consistent with MPN. Lymph node histology and immunophenotyping usually confirm a T cell lymphoblastic lymphoma [6,8-10], whereas B lymphoblastic leukemia/lymphoma is uncommon, with only 8 reported cases [11]. Myeloid sarcoma has also been described [1].

Our case presented with the atypical clinical appearance of the EMS, having in mind the presence of epistaxis as first symptom and development of mediastinal lymphadenopathy during disease progression. Of all patients reported, approximately 2/3 had localized or generalized lymphadenopathy, but only a few had a mediastinal mass [7]. Comparing our patient with the patient described by Still et al. both were younger males with constitutional symptoms, increased hemoglobin levels, low platelet counts, and left shifts, with 9% and 11% eosinophils, respectively [7]. The bone marrow biopsies for both patients showed hypercellular marrows consistent with aMPN, and cytogenetic analyses confirmed t(8;13) (p11;q12) in both cases.

What is the main trigger for oncogeneisis in EMS? Disruption of the fibroblast growth factor receptor 1 (FGFR1) gene at the 8p11-12 chromosomal locus, and creation of novel fusion genes and chimeric proteins usually result in constitutive activation of FGFR1 tyrosine kinase. Various partner genes foster dimerization of FGFR1 protein and promote activation of downstream signaling pathway resulting in oncogenesis. To date, 13 translocations and 1 insertion involving chromosome 8p11 have been identified [9], as well as 12 partner genes [12,13]. Zinc finger, MYM-type 2 (ZMYM2) gene, located at chromosome 13q12, is the most frequent partner gene, and is associated with the fusion gene in nearly 50% of the cases [1]. Disruption occurs in introns 14 and 8 of the ZMYM2 and FGFR1 genes, respectively, followed by fusion of exon 14 of ZMYM2 to exon 9 of FGFR1. This novel gene encodes a fusion protein composed of 9 zinc-finger motifs and proline-rich domain of the ZMYM2 protein with the cytoplasmic tyrosine kinase domain of FGFR1 [14,15]. All of the fusion transcripts studied have been shown to have constitutive, ligand-independent tyrosine kinase activity, with the ability to transform Ba/F3 murine hematopoietic cell lines [2]. Constitutional tyrosine kinase activity leads to activation of several effector pathways, including STAT1 and STAT5, PI3K, PLC-γ and MAP-kinase [16].

EMS is incurable in most patients with overall survival of 15 months, as it evolves into chemo-resistant AML. Various therapeutic modalities have been applied, including chemotherapeutic protocols for acute leukemia or chronic myeloid neoplasms, but the results are discouraging. Overall response to these protocols ranged from progressive disease to short-term complete remission [1,9]. The only potential curative therapeutic option for these patients seems to be allo-SCT. For the 45 EMS patients so far described with follow-up, 14 (51%) underwent bone marrow or stem cell transplantation: 12 (27%) after leukemic transformation and 2 (4%) before transformation. Median survival for those patients who underwent transplant after transformation was 24 months, with a range between 6 and 46 months [1]. However, the median survival was only 12 months for those who did not receive a transplant (log rank, p=0.0167), with a range between 0 to 60 months [1].

Novel agents targeting constitutive tyrosine kinase activity and downstream pathway members are being developed [16]. The tyrosine kinase inhibitor ponatinib (AP24534) specifically reduced the numbers of FGFR1-fusion gene positive colonies, showing considerable promise for the treatment of patients with EMS [17]. But the increasing frequency of reported side effects as well as heart attacks resulting in death, worsening coronary artery disease, stroke, narrowing of large arteries of the brain, severe narrowing of blood vessels in the extremities requires careful evaluation of the risks and benefits for each patient who is candidate for ponatinib [18].

Conclusion

Patients with MPN and translocations involving chromosome 8 need to be carefully evaluated for EMS. However, despite new therapeutical agents being developed, allo-SCT remains the only potential curative option.

Conflict of interests

The authors declare no conflict of interests.
References


