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SHORT COMMUNICATION

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.

Herein we describe a 22-year-old male patient with unusual clinical presentation of EMS. Namely, he initially presented with prolonged epistaxis. Complete blood count showed elevated hemoglobin (17.7g/dl), thrombocytopenia (98x10^9/l) and leukocytosis (57x10^9/l). Bone marrow aspirate and biopsy findings corresponded with the presence of a myeloproliferative neoplasm while cytogenetic analysis revealed t(8;13)(p11q12). After that ZMYM2-FGFR1 in-frame fusion was confirmed at the molecular level.

Immediately after establishing the diagnosis of a myeloproliferative neoplasm (MPN) generalized lymphadenopathy was developed. Histopathologic examination of lymph node sample confirmed the diagnosis of a T cell lymphoblastic lymphoma without bone marrow involvement. Four cycles of Hyper CVAD chemotherapy were administered with complete morphological and cytogenetic remission. Four weeks after evaluation, patient developed peripheral blood monocytosis and eosinophilia without bone marrow criteria for acute leukemia. Cytogenetic analysis showed t(8;13) accompanied by complex numerical and structural aberrations. The patient underwent allogeneic stem cell transplantation (allo-SCT) from HLA matched sister and he subsequently achieved complete remission.

In conclusion, patients with MPN and translocations involving chromosome 8 need to be carefully evaluated for EMS. However, having in mind the very aggressive clinical course of EMS allo-SCT is the only potential curative option.

Introduction and Results

8p11 (eight p11) 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, peripheral blood eosinophilia in the absence of basophilia, and a reciprocal translocation involving chromosome 8p11 [1,2]. 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 637 IU/l (range 135-

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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

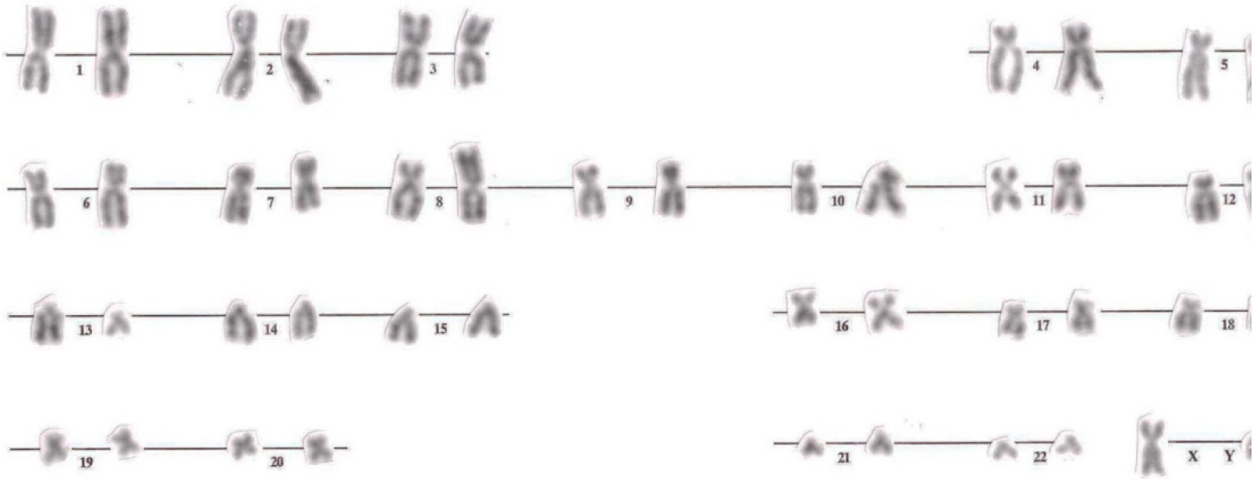

Figure 1a. t(8;13)(p11q12).

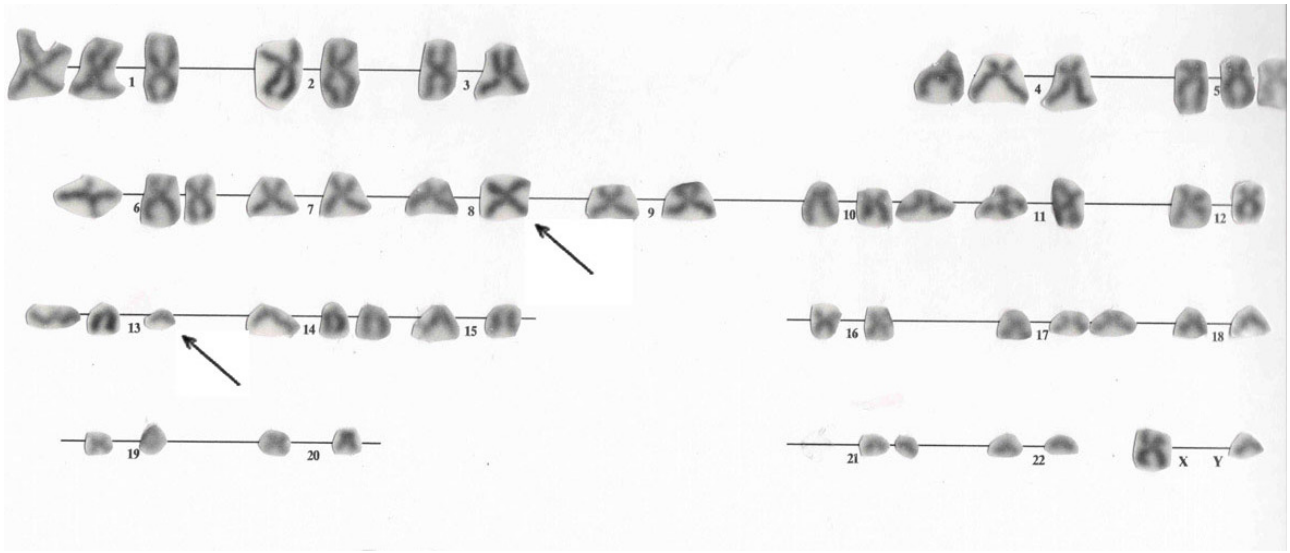

Figure 1b. t(8;13) accompanied by complex numerical and structural aberrations. Arrows show basic structural aberration of t(8;13) (p11;q12) among other structural and numerical aberrations which arose during disease evolution.

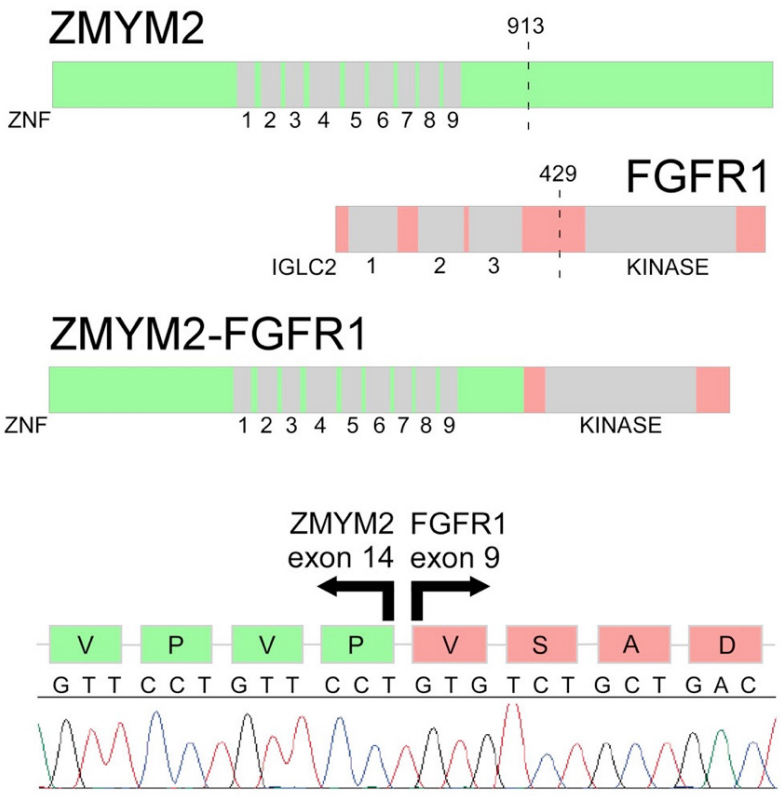

Figure 2. The protein structures of normal ZMYM2, normal FGFR1 and chimeric ZMYM2-FGFR1 are depicted. The domain structures were taken from the UniprotKB/Swiss-Prot Database. Numbers above the structures indicate the aminoacid position of the breakpoint. The new fusion transcript results from an in-frame 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.

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-

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 (31%) 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 confict of interests.

References

1. Jackson CC, Medeiros LJ, Miranda RN. 8p11 myeloproliferative syndrome: a review. Hum Pathol 2010;41:461-476.
2. Goradia A, Bayerl M, Cornfield D. The 8p11 Myeloproliferative Syndrome: Review of Literature and an Illustrative Case Report. Int J Clin Exp Pathol 2008;1:448-456.
3. Kuskonmaz B, Kafali C, Akcoren Z, Karabulut HG, Akalin I, Tuncer MA. The 8p11 myeloproliferative syndrome in a 3-year-old child. Leuk Res 2008;32:198-199.
4. Friedhoff F, Rajendra B, Moody R, Alapatt T. Novel reciprocal translocation between chromosomes 8 and 9 found in a patient with myeloproliferative disorder. Cancer Genet Cytogenet 1983;9:391-394.
5. Roy S, Szer J, Campbell LJ, Juneja S. Sequential transformation of t(8;13)-related disease: a case report. Acta Haematol 2002;107:95-97.
6. Abruzzo LV, Jaffe ES, Cotelingam JD, Whang-Peng J, Del Duca Jr V, Medeiros LJ. T-cell lymphoblastic lymphoma with eosinophilia associated with subsequent myeloid malignancy. Am J Surg Pathol 1992;16:236-245.
7. Still IH, Chernova O, Hurd D, Stone RM, Cowell JK. Molecular characterization of the t(8;13)(p11;q12) translocation associated with an atypical myeloproliferative disorder: evidence for three discrete loci involved in myeloid leukemias on 8p11. Blood 1997;90:3136-3141.
8. Catovsky D, Bernasconi C, Verdonck PJ et al. The association of eosinophilia with lymphoblastic leukaemia or lymphoma: a study of seven patients. Br J Haematol 1980;45:523-534.
9. Li F, Zhai YP. 8p11 myeloproliferative syndrome. Zhongguo Shi Yan Xue Ye Xue Za Zhi 2013;21:1073-1077.
10. Yan Z, Yang B, Wang QS et al. Clinical pathological features of the 8p11myeloproliferative syndrome. Zhongguo Shi Yan Xue Ye Xue Za Zhi 2010;18:1321-1326.
11. Trimaldi J, Carballido EM, Bowers JW et al. B-Lymphoblastic Leukemia/Lymphoma Associated with t(8;13)(p11;q12)/ ZMYM2 (ZNF198)-FGFR1 : Rare Case and Review of the Literature. Acta Haematol 2013;130:127-134.
12. Yang JJ, Park TS, Choi JR et al. Submicroscopic Deletion of FGFR1 Gene Is Recurrently Detected in Myeloid and Lymphoid Neoplasms Associated with ZMYM2-FGFR1 Rearrangements: A Case Study. Acta Haematol 2012;127:119-123.
13. Li F, Zhai YP, Tang YM, Wang LP, Wan PJ. Identification of a novel partner gene, TPR, fused to FGFR1 in 8p11 myeloproliferative syndrome. Genes Chromosomes Cancer 2012;51:890-897.
14. Reiter A, Sohal J, Kulkarni S et al. Consistent fusion of ZNF198 to the fibroblast growth factor receptor-1 in the t(8;13)(p11;q12) myeloproliferative syndrome. Blood 1998;92:1735-1742.
15. Xiao S, Nalabolu SR, Aster JC et al. FGFR1 is fused with a novel zinc-finger gene, ZNF198, in the t(8;13) leukaemia/lymphoma syndrome. Nat Genet 1998;18:84-87.
16. Chase A, Grand FH, Cross NC. Activity of TKI258 against primary cells and cell lines with FGFR1 fusion genes associated with the 8p11myeloproliferative syndrome. Blood 2007;110:3729-3734.
17. Chase A, Bryant C, Score J, Cross NC. Ponatinib as targeted therapy for FGFR1 fusions associated with the 8p11 myeloproliferative syndrome. Haematologica 2013;98:103-106.
18. U.S. Food and Drug Administration http://www.fda.gov.htm Accessed October 31, 2013.