

Myeloid and lymphoid neoplasms with FGFR1 rearrangement—one case report and lecture review

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Abstract: We report one case of myeloid and lymphoid neoplasms with FGFR1 rearrangement (EMS) here. The patient presented with generalized lymphadenopathy and fever. The bone marrow aspirates indicated CML but karyotype analysis discovered the translocation of t(8;13)(p11;q12), not t(9;22) and the BCR-ABL fusion transcript was not found. The histology was T-cell lymphoblast lymphoma (LBL) from the lymph node biopsy. Therefore the diagnosis of EMS was made. After chemotherapy, bone marrow assessment improved and most of the lymph nodes shrunk to undetectable. But the t(8;13) still remained. From the lecture review, we can see that on most occasions EMS presents as an atypical myeloproliferative disease characterized by myeloid hyperplasia, eosinophilia, translocation always involves the band 8p11 and high incidence of T-LBL. The fibroblast growth factor receptor-1 which locates at 8p11 is broken and fuses the other partner gene to start the malignant transformation. By now, only allogeneic stem cell transplantation appears to cure.

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[Key words] Myeloproliferative disease; Eosinophilia; 8p11; Lymphoma; Fibroblast growth factor receptor-

Introduction

Myeloid and lymphoid neoplasms with FGFR1 rearrangement, which is originally named as 8p11 myeloproliferative syndrome (EMS), is a rarely happened hematological malignancy characterized by myeloid hyperplasia, eosinophilia, high incidence of lymphoblast lymphoma (LBL). The chromosome translocation always involves the band 8p11 where is the locus of fibroblast growth factor receptor-1 (FGFR1). The fusion protein constitutively activates the tyrosine kinase and influences the cell growth, differentiation, apoptosis through several signal transduction pathways. So far, more than forty cases were reported but seldom in China^[1,2]. Here we report one case we found with lecture review.

Case information

In June of 2007, the 7 year old boy had been found with lymphadenectasis in bilateral neck and in July of 2008, the boy got fever with the temperature 39--40 and the lymphadenectasis spread to many parts of the body. He was treated as lymphadenitis in local hospital with antibiotics for 10 days (name and dose of the medicine unclear) and the results were unsatisfactory. The complete blood count (CBC) in another hospital showed WBC $74.58 \times 10^9/L$, hemoglobin 139g/L, platelet count $208 \times 10^9/L$ and one course of oral hydroxycarbamide followed by one course of intravenous ara-C was given because chronic myelogenous leukemia (CML) was suspected from bone marrow aspirate. Because of the poor effect of the treatment, the patient came to our hospital. The

physical examination showed the lymphadenectasis in the lower mandible, neck, armpit and inguinal. Sternum tenderness and splenohepatomegalia were also found. The blood smear showed a prominent myeloid left shift and eosinophilia with 1% promyelocyte, 3% myelocytes, 7% metamyelocytes, 3% bands, 48% neutrophils and 10% eosinophils. Bone marrow aspirate showed an extremely hypercellular marrow with 77.2% of myeloid lineage including 4% myeloblasts, 4% promyelocytes, 20.8% myelocytes, 12% metamyelocytes, 20.4% bands and 5.2% neutrophils and 9.6% eosinophils (**Figure 1**). The score of neutrophil alkaline phosphatase was 71 with 50% positive cells. Cytogenetic analysis of the bone marrow aspirate showed the following karyotype: 46, XY, t(8;13)(p11;q12)[20] (**Figure 2**), and the BCR-ABL fusion transcript was not found. Biopsy of the lymph node demonstrated diffuse infiltrate composed of intermediate-sized mononuclear cells with scant cytoplasm and large round nuclei with fine chromatin. Immunohistochemical stains showed that these cells were positive for CD3, CD99, CD43, terminal deoxyribonucleotidyl transferase (TdT) and negative for CD20, Pax-5, consistent with a diagnosis of T lymphoblastic lymphoma (T-LBL) (**Figure 3a-3f**). Combining the excessive myelopoiesis of the bone marrow, diagnosis of T-LBL and the chromosome karyotype, it was concluded that the patient had the myeloid and lymphoid neoplasms with FGFR1 rearrangement^[3].

The patient began his treatment in our hospital with 2 courses of CHOPE (cyclophosphamide,

vincristine, etoposide, prednisone)^[4], and achieved a partial remission. The bone marrow aspirate showed 0.4% myeloblast, 0.8% promyelocyte, 9.2% myelocytes, 9.6% metamyelocytes, and 7.6% eosinophils and the total myeloid lineage count 52.4%. The CBC showed WBC $4.31 \times 10^9/L$, hemoglobin 84 g/L, platelet count $236 \times 10^9/L$. The lymphadenectasis and splenohepatomegalia were eased and the fever stopped. But the karyotype of t(8;13)(p11;q12) of the bone marrow aspirate still remained. From September to November, we gave the patient 3 course of Hyper-CVAD(cyclophosphamide, vincristine, doxorubicin and dexamethasone)^[5], repeat bone marrow aspiration, cytogenetic analysis, CBC and clinical condition showed no further improvement.

Discussions and lecture review

When we review the reports, we can see that in 1983, there were 2 cases of myeloproliferative disease(MPD) with the chromosome translocation of t(8;9)(p11;q33-34). They were finally diagnosed as Ph

chromosome negative CML^[6,7]. In 1992, Abruzzo and his colleagues summarized the main characteristics of the disease in his 3 cases report: bcr/abl negative MPD usually accompanied by precursor T-LBL, eosinophilia and the chromosome translocations always involving 8p11, where is the locus of FGFR1^[8]. Macdonald gave out the name of the disease, 8p11 myeloproliferative syndrome(EMS) in 1995^[9] and in the WHO Classification of Tumors of Haematopoietic and Lymphoid Tissue in 2008, EMS was redefined as myeloid and lymphoid neoplasms with FGFR1 rearrangement. The abnormality of 8p11 translocation can be found present in both the myeloid and lymphoid malignancies suggests that the pluripotent stem cell is the target of transformation^[10]. So this disease is also called stem cell leukemia/lymphoma syndrome (SCLL). The rearrangements disrupt the FGFR1 gene at chromosome 8p11 and form fusion transcripts with different partner genes. So far, 8 partner genes have been identified in association with FGFR1 rearrangements in EMS (Table 1).

Table 1 Translocations and FGFR1 gene fusion partners in EMS

Translocation	FGFR1 gene fusion partner	References
t(8;13)(p11;q11-12)	ZNF198	Xiao et al ^[11]
t(6;8)(q27;p11)	FOP/FGFR1OP	Popovici C et al ^[13]
t(8;9)(p11;q33)	CEP110	Guasch G et al ^[12]
t(8;22)(p11;q22)	BCR	Fioretos T et al ^[14]
t(8;19)(p11;q13)	HERV-K	Guasch G et al ^[15]
ins(12;8)(p11;p11p21)	FGFR1OP2	Grand EK et al ^[16]
t(7;8)(q34;p11)	TIF1	Belloni E et al ^[18]
t(8;17)(p11;q23)	MYO18A	Walz C et al ^[17]

All the partner genes are fused to the exon 9 of FGFR1 with the cytoplasmic tyrosine kinase domain of FGFR1. So EMS and CML share a common molecular pathogenesis in that they both involve tyrosine kinase fusion genes. FGFR1 normally exists as monomeric plasma membrane proteins that dimerize upon ligand binding of fibroblast growth factors and transducer intracellular signals via phosphorylated signaling intermediates. And the most common translocation associated with EMS, the t(8;13), fuses FGFR1 with the partner gene ZNF198, which locates at 13q11. It is composed of five zinc finger domains and a proline-rich domain. Both of the domains are conserved in the fusions and the proline-rich domain is essential for the oligomerization of the fusion protein, and makes the FGFR1 fusions exhibit aberrant tyrosine kinase activity. Subsequent activation of various downstream signal transduction pathways, notably STAT 5, culminates in unregulated cell proliferation and neoplastic transformation^[19,20]. It is similar with FOP-FGFR1 through PLC- 、

MAPK/ERK 、 PI3K/AKT/mTOR pathways and BCR-FGFR1 through STAT5, MAPK pathways in cell transformation^[21,22].

Clinical phenotype

Marked leukocytosis in the peripheral blood can usually be found at presentation and the predominant cell types are neutrophils, metamyelocytes and myelocytes, similar to CML in certain aspects. Eosinophilia is a distinguishing feature of EMS and is seen in 90% patients in either bone marrow, peripheral blood or both. The bone marrow showed myeloid hyperplasia in most cases while certain variability were also found. Some cases, especially those with t(8;9) resembled chronic myelomonocytic leukemia but without major dysplastic signs in either lineage^[17,23,24]. Several cases had the marrow findings of AML at the time of diagnosis of EMS while few had ALL or bilineal acute leukemia^[14, 25 26,27]. One of the most striking finding of EMS is the high frequency of LBL which is seen in more than two thirds of EMS

cases and the patients with t(8;13) had a higher incidence than other translocations^[28]. The histology findings shows that most cases demonstrate the feature of T-LBL while few present the findings of myeloid sarcoma^[29,30]. EMS has a natural history similar to CML in that both of them have a chronic phase. But median duration of it for EMS lasts only 6~9 months and most patients progress to AML or less commonly, B-lineage ALL without effective treatment^[31].

Treatment

Up to now, only stem cell transplantation(SCT) offers the prospect of cure because the malignancy can not be eradicated by conventional chemotherapy. In the absence of SCT, disease progression was observed in the vast majority of cases and most patients died from resistant disease or early relapse within 1.5 years of diagnosis. Because of the obvious effect of imatinib to CML, much efforts are putting on the research of similar tyrosine kinase inhibitor. PKC412 (N-benzoylstaurosporine) is a small molecule tyrosine kinase inhibitor of many protein kinases and was shown to inhibit ZNF198-FGFR1 activity in cell lines. In the mouse model of EMS, the group of PKC412 had prolonged survival than control group. For a EMS patient with t(8;13), the treatment of PKC412 led to both dramatic decrease of phosphorylated tyrosine and clinical control of the disease in 6 month before SCT^[32]. These results raised the possibility that small molecule tyrosine kinase inhibitor that specially target FGFR1 fusion proteins may be available in the future for EMS patients.

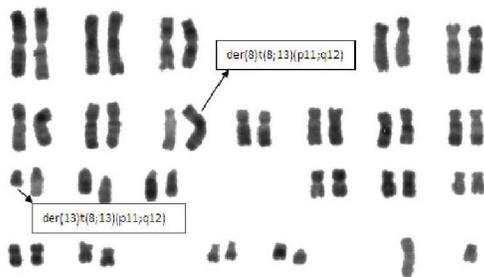


Figure 1. Bone marrow aspirate with myeloid hyperplasia and eosinophilia (Wright's-Giemsa Stain, ×1000)

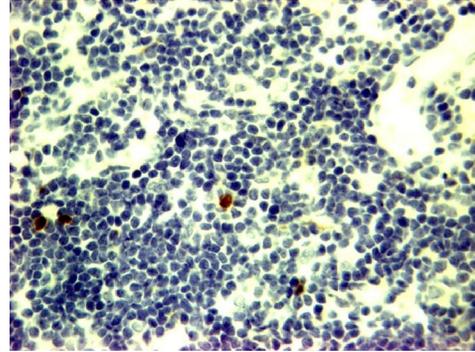


Figure 2. Chromosome translocation t(8;13)(p11;q12)

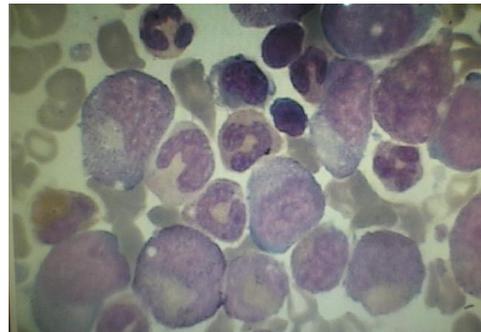


Figure 3a. Lymphoma cells negative for Pax5 (Immunohistochemical SP stain, ×400)

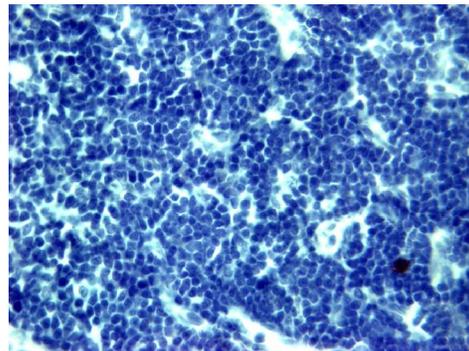


Figure 3b Lymphoma cells negative for CD20 (Immunohistochemical SP stain, ×400)

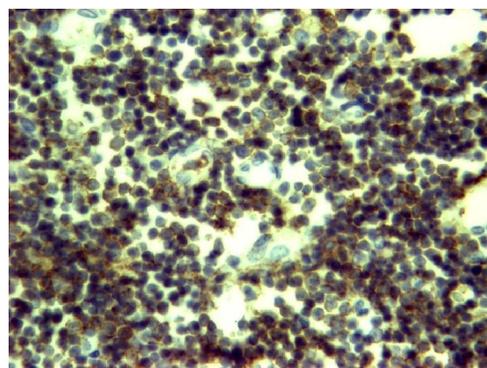


Figure 3c Lymphoma cell membrane positive for CD43 (Immunohistochemical SP stain, ×400)

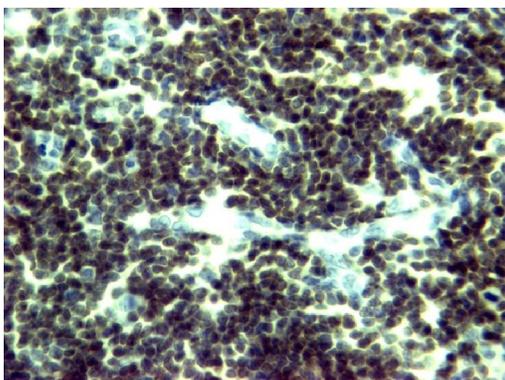


Figure 3d Lymphoma cell membrane positive for CD3 (Immunohistochemical SP stain,×400)

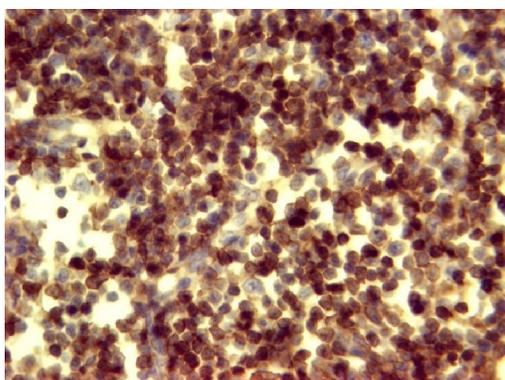


Figure 3e. Lymphoma cell membrane positive for CD99 (Immunohistochemical SP stain,×400)

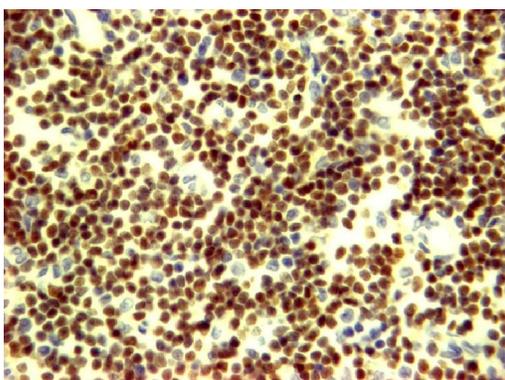


Figure 3f Lymphoma cell nuclei positive for TdT (Immunohistochemical SP stain,×400)

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