Case Report

Lympho-myeloproliferative disorder without 8p11 chromosomal abnormality

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Abstract

We report here a case of myeloproliferative disorder accompanied by T-cell lymphoma and eosinophilia. Both bone marrow cells and lymphnode cells showed the same complicated chromosomal abnormalities, suggesting that transformation of stem cells might have been involved in the development of both myeloproliferative disorder and T-cell lymphoma in this patient. This is a rare case in which clinical features resemble those of 8p11 myeloproliferative syndrome/stem-cell myeloproliferative disorder but its characteristic chromosomal abnormalities involving 8p11 were not found. The mechanisms of the simultaneous development of myeloproliferative disorder and T-cell lymphoma by stem cell transformation are of immense interest.

(Key words: myeloproliferative disorder, T-cell lymphoma, mastocytosis, Stem-cell myeloproliferative disorder)

Introduction

8p11 myeloproliferative syndrome (EMS)/stem-cell myeloproliferative disorder is a rare disease characterized by myeloproliferative disease with eosinophilia accompanied by lymphoid malignancy. Constitutive activation of FGFR1, which is one of the transmembrane tyrosine kinase receptors for fibroblast growth factor and is located at 8p11, may be involved in progression of the disorders¹. There has been no report of a case with the clinical features resembling those of EMS but having no chromosomal abnormalities involving 8p11. We report here a rare case of myeloproliferative disorder accompanied by T-cell lymphoma and eosinophilia in which chromosomal translocation involving 8p11 was not found.

Case Report

A 21-year-old man was referred to a hospital because of cervical lymphnode swelling that had persisted for one week. Hematologic examination revealed leukocytosis (53, 120/µl) with 9% myeloblasts, 18% myelocytes, 28% neutrophils, 15% eosinophils, 3% monocytes and 41%

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lymphocytes. Hemoglobin concentration was 17.6 g/dl and platelet count was 9.3x10⁴/μl. Laboratory examination disclosed a low neutrophil alkaline phosphatase score (125) (normal 170-335) and high level of vitamin B₁₂ (1170 pg/ml) (normal 243-894). The bone marrow was hypercellular with abundant myeloid cells (M/E ratio, 6.2), including 27% eosinophils and 0.8% mast cells. Chromosomal analysis of bone marrow cells revealed 47, XY, -8, add(11) (q23), t(13:17) (q12;q23), add(16) (q22), +der(?) t(?;8) (?;q11)×2[5]/48, idem, +19[7]. Neither major nor minor BCR/ABL transcripts were detected by reverse transcription polymerase chain reaction. Based on these findings, the patient was diagnosed as having myeloproliferative disease (MPD) with eosinophilia. No medication was given at that time because he initially showed no clinical symptoms.

However, three months after initial diagnosis had been made, high fever, generalized lymphadenopathy and marked splenomegaly appeared. The histological examination of the biopsy sample of an inguinal lymphnode demonstrated the region with many medium-large sized atypical lymphcytes (Fig. 1A, 1B). These lymphcytes were positive for CD3 and MIB-1, which were representative markers of T-cells. Furthermore, a rearrangement of T-cell receptors was revealed by Southern blot analysis of the biopsy sample (data not shown). Based on these findings, a diagnosis of T-cell lymphoma was made. Cytogenetic analysis of the lymphnode showed the same abnormal karyotype as that observed in bone marrow cells at the time of the initial examination. The patient was first treated with a combination of hydroxyurea and prednisolone. Following this therapy, leukocyte count rapidly declined and both the high fever and general lymphnode swelling were simultaneously improved (Fig. 2). However, high fever and generalized lymphadenopathy recurred five months after the start of treatment. Another regimen of chemotherapy using methylprednisolone, cytosine arabinoside and etoposide was performed, but it was not effective. In addition, severe skin rash appeared during chemotherapy. The patient was then referred to Jichi Medical School Hospital.

Laboratory tests carried out on admission to Jichi Medical School Hospital showed a high
level of serum tryptase, which is specifically released from mast cells. In addition, the number of cells with centrally located round-shaped nuclei in bone marrow was increased (26% of all nucleated cells). These cells were positive for both acid phosphatase and PAS staining and showed metachromasia after toluidine blue staining. Based on these results, the cells were considered to be mast cells. Chromosomal and sequence analyses showed normal karyotype and no point mutations of the c-kit gene, respectively, in bone marrow cells. After treatment with high dose-cytarabine and mitoxantrone, lymphnode swelling was significantly improved and the skin eruption disappeared. After 7 days of treatment, however, a large number of mast cells still remained in bone marrow (83% of NCC). Moreover, thrombocytopenia worsened, with a platelet count of 7,000/\mu L, and he died of lung hemorrhage after 18 days of treatment.

**Discussion**

We have described a case of myeloproliferative disorder with eosinophilia accompanied by T cell lymphoma. Mastocytosis also developed during the clinical course. Abruzzo et al. first reported a patient with myeloproliferative disorders accompanied by eosinophilia and lymphoid malignancy with chromosomal translocations involving 8p11\(^3\). Since then, several cases showing the same features have been reported\(^3\)\(^9\)\(^9\), and the condition has been named 8p11 myeloproliferative syndrome (EMS)/stem-cell myeloproliferative disorders. Previous studies showed that constitutive activation of FGFR1 may be involved in progression of the disorders\(^3\). FGFR1 is located at 8p11 and has been reported to form various kinds of fusion genes with FOP
at 6q27, with CEP110 at 9q33, with FIM/ANF198 at 13q12 and with BCR at 22q11 through chromosomal translocations. Since chromosomal translocation involving 8p11 was not found in our patient, a diagnosis of EMS could not be made. It is notable, however, that an inguinal lymphnode had the same complicated chromosomal abnormalities as those observed in bone marrow cells at the time of the initial examination. Since myeloid lineage cells in a biopsy sample of an inguinal lymphnode were not contaminated, these results strongly suggest that the transformation of stem cells might have been involved in the development of both myeloproliferative disorder and T-cell lymphoma. Thus, the pathophysiology as well as clinical features of this case resembled those of EMS. It is of importance to elucidate the molecular mechanisms involved in the development of this patient’s disorder. It is noteworthy that there were complicated chromosomal abnormalities, including 13q12, which is one of the partners of 8p11 in chromosomal translocation in EMS. Since FIM/ANF198 protein may play an important role in the development of hematopoiesis in mouse aorta-gonad-mesonephros region, it is possible that 13q12 abnormality is involved in the development of this patient’s disorder.

Another chromosomal abnormality, 16q22, was also observed in the patient. Since 16q22 is known to be associated with eosinophilia complicated by some type of acute myeloid leukemia, it is conceivable that this chromosomal abnormality was related to the eosinophilia in the patient.

In our patient, mastocytosis emerged with progression of his disease. Systemic mastocytosis, in which mutations of the c-kit gene are commonly observed, is sometimes associated with various hematological diseases. In addition, reactive non-clonal proliferation of mast cells is also observed in some hematopoietic stem cell diseases and lymphoproliferative diseases. In this case, no mutation of the c-kit gene was found in bone marrow cells. Furthermore, an abnormal karyotype was not found in bone marrow cells after mastocytosis had occurred. Thus, it is possible that the increase in mast cells was not monoclonal but rather due to the result of reactive non-clonal proliferation. Since heparin is one of the chemical mediators released from mast cells, it is likely that not only thrombocytopenia but also an increase in the local concentration of heparin from lung-infiltrating mast cells caused lung hemorrhage, which was the cause of his death.

To the best of our knowledge, this is the first report of a case showing clinical features similar to those of EMS without any involvement of 8p11 chromosomal abnormalities. The mechanisms of the simultaneous development of myeloproliferative disorder and T-cell lymphoma by stem cell transformation are of great interest.

References
8p11関連の染色体異常を伴わない
Lympho-myeloproliferative disorder

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要 約

症例はT細胞性リンパ腫と好酸球増多を合併した骨髄増殖性疾患の21歳の男性。骨髄細胞とリンパ節生検から得られた細胞とで共通の複雑な染色体異常を認めたことから、造血幹細胞レベルでの腫瘍化が骨髄増殖性疾患およびT細胞性リンパ腫の発症に関わっているものと推察された。同様の臨床所見を示す疾患として、8p11 myeloproliferative syndrome (EMS)/stem-cell myeloproliferative disorderが知られているが、本症例は8p11関連の染色体異常を認めないことから、異なった機序により発症したものと考えられる。