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Initial Symptom of Upper Respiratory Infection in Chronic Eosinophilic Leukemia with FIP1L1/PDGFRA Rearrangement: Recovery with Iimatinib

Keyu Liu[1], Yanfang Yu[2], Huijuan Song[3], Xueqin Wang[1], Zexian Fu[4*]
[1]Departments of Clinical Laboratory, Affiliated Hospital of Engineering University of Hebei, Hebei, 056002, China
[2]Departments of Hematology, Affiliated Hospital of Engineering University of Hebei, Hebei, 056002, China
[3]Departments of Laboratory, Affiliated Zhongshan Hospital of DAlian University, Liaoning, 116001, China
[4]Departments of Science and Education, Affiliated Hospital of Engineering University of Hebei, Hebei, 056002, China
*Corresponding author

Abstract: This article intended to present and analyze a patient with factor interacting with PAPOLA and CPSF1/platelet-derived growth factor receptor α(FIP1L1/PDGFRA)-associated chronic eosinophilic leukemia (CEL) to probe the characteristics in the diagnosis, treatment, and prognosis of the disease. Methods: We retrospectively analyzed the clinical data of a patient with FIP1L1/PDGFRA-positive CEL. Results: Clinical features of the case is upper respiratory infection as initial symptom. The patient presented with increased white blood and eosinophil count in peripheral blood, mild anemia, multiple lymph node enlargement, splenomegaly, and cytogenetic variation of positive FIP1L1/PDGFRA. Conclusion: The clinical features of CEL is clonal proliferation of eosinophil, The peripheral blood and bone marrow are always involved. Tissue infiltration by eosinophils and the release of cytokines and humoral factors from the eosinophil granules result in damage of tissue in numbers of organs. Gene targeting treatment using imatinib led to quick and effective recovery for the Patient.

Keywords: Chronic eosinophilic leukemia; FIP1L1/PDGFRA; Imatinib; Upper respiratory infection

1. Introduction

CEL with FIP1L1/PDGFRA rearrangement is a rare reason of hypereosinophilia, and there are only few reports in China. A patient presented with FIP1L1/PDGFRA-positive CEL was treated in the haematology department of our hospital. Gene targeting treatment using imatinib led to quick and effective recovery for the patient after the diagnosis was established.

2. Case Report

A previously healthy 40-year-old man sought medical attention in February 2017 with a half-year history of elevated eosinophil count in peripheral blood and 4-day history of cough and expectoration. The tests of all antibody for parasites were negative and no allergic symptoms were present. On physical examination, the doctor observed there was no haemorrhage into the skin and mucous membrane. Laboratory findings were as follows: WBC (white blood cell count) was 18.1 × 109/l, HB (hemoglobin) was 106 g/l, platelet count was 129 × 109/l, eosinophil count was 11.9 × 109/l, autoantibodies tests were negative, LDH (lactate dehydrogenase) was 342 U/L, hsCRP (high-sensitivity C-reactive protein) was 25.84 mg/l, ferritin was 485.15 ng/ml, folate was 4.12 ng/ml, and vitamin B12 > 2000 pg/ml. Enlarged multiple lymph nodes in the armpits, splenomegaly, streaky or coarse reticular pattern of the right middle lobe, and reduced density of heart shadow were detected by computed tomography.

Peripheral blood smear revealed eosinophils were significantly increased [Figure 1].

Bone marrow aspirate revealed obvious proliferation of granulocyte and marked eosinophilia, often with bizarre nuclear lobulation, and dysgranulation. (Figure. 2).

BM biopsy indicated obvious proliferation of granulocyte. Granulocytes were visible at each stage and mainly at the middle and late stage.The proportion of eosinophil markedly elevated. No obvious abnormal precursor cells were observed. The proportion of erythrocyte was low. The number of megakaryocytes was approximately normal. There were a small amount of lymphocytes and plasma cells, scattering in the BM. There was no obvious proliferation of fibrous tissue. Immunophenotypic analysis of BM aspirate by flow cytometry confirmed the cell population of eosinophils with 37.52% of nucleated cells.

The cell population was positive for CD13, CD11b, CD10, CD15, CD9 and CD16. A few cells expressed CD64, CD33 and CD38. Cytogenetic analysis of the bone marrow cells confirmed a 46, XY(20) karyotype. WT1 gene expression analysis by fluorescent quantitative PCR (polymerase chain reaction) revealed that 0.05% of the cells were positive for WT1 gene expression (WT1-positive standard: >2% of positive cells). The detection of myeloproliferative neoplasms-associated gene confirmed the patient did not harbor JAK2 14exon, JAK2 12exon, MPL 10exon and CALR 9exon mutations. FISH (fluorescence in situ hybridization) analysis was positive for FIP1L1/PDGFRA, and negative for TEL-PDGFRB and TEL-ABL fusion gene. According to the 2017 World Health Organization classification, he was diagnosed with FIP1L1/PDGFRA-positive CEL[1-3].

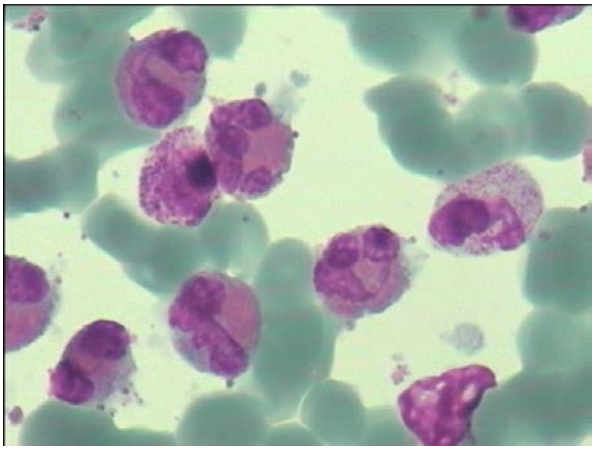

Figure 1. Morphology of peripheral blood smear revealed eosinophils were significantly increased(Wright-Giemsa, ×1000).

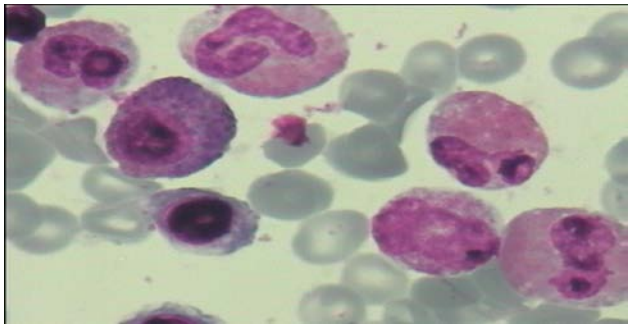

Figure 2. Morphology of bone marrow aspiration revealed obvious proliferation of granulocyte and marked eosinophilia, often with bizarre nuclear lobulation, and dysgranulation.(Wright-Giemsa, ×1000).

At first, he was treated with methylprednisolone and he didn't show obvious decrease of eosinophil. Then, treatment using hydroxycarbamide and methylprednisolone bigan. However, it seems he still didn't get better. Treatment using Low-dose imatinib (200 mg/d) was started after the diagnosis of CEL associated with FIP1L1/PDGFRA. The primary symptoms in respiratory system such as cough and expectoration gradually disappeared. The eosinophil and White blood cell (WBC) count declined gradually to normality within 3 weeks of treatment using imatinib. BM aspiration revealed normal cells of marrow with 2.0 % of eosinophil count. FIP1L1/PDGFRA fusion gene of the patient became negative after 3 months of treatment. The patient took low-dose imatinib (100 mg) every other day as consolidation therapy and he had no symptoms and signs for over a year.

3. Discussion

The most common myeloproliferative neoplasm associated with PDGFRA rearrangement is that associated with FIP1L1-PDGFRA gene fusion. These neoplasms generally present as CEL. CEL associated with FIP1L1-PDGFRA is a multisystem damage.[4-5] The peripheral blood and bone marrow are always involved. Tissue infiltration by eosinophils and the release of humoral factors and cytokines from the eosinophil granules result in disorder of a number of organs; central and peripheral nervous system, the heart, lungs, gastrointestinal tract and skin are commonly involved. The peripheral blood eosinophil count is usually markedly elevated.[-5]There is no BCR-ABL1 fusion gene or Philadelphia (Ph) chromosome. If there is no evolution to AML (acute myeloid leukaemia), blasts in bone marrow and the peripheral blood are less than 20%. Bone marrow aspirate and cytogenetic analysis, bone marrow biopsy and investigation for FIP1L1/PDGFRA are needed for the diagnosis of CEL. Because blast cells of most patients aren't increased or conventional cytogenetic analysis of them is normal , it is in general the determination of the FIP1L1-PDGFRA fusion gene that makes the correct diagnosis of CEL. Abnormal cytogenetic analysis appears to be more common when transformation to acute leukaemia has occurred.[6-8]

Patients with FIP1L1/PDGFRA-associated CEL often present with pruritus, fatigue, gastrointestinal, respiratory, or cardiac symptoms.Some patients have no obvious symptoms at diagnosis, but most of the patients have splenomegaly and some present with hepatomegaly or enlarged multiple lymph nodes. Endomyocardial fibrosis, with following restrictive cardiomyopathy is the most serious clinical symptoms. Scarring of the mitral and/or tricuspid valves leads to valvular regurgitation and the formation of intracardiac thrombi, which may embolize. The patients may suffer venous thromboembolism and arterial thromboses. Symptoms of Pulmonary disease include cough and dyspnoea, and the disease is restrictive and relative to fibrosis. Sometimes the patients present with thrombocytopenia and anaemia.[9-11] The eosino-

phil morphology of many cases of FIP1L1/PDGFRA-associated CEL is normal approximately. Only a few patients show increased blast cells in the peripheral blood. Eosinophil count from the peripheral blood is usually markedly elevated and neutrophil count is always increased. However, monocyte and basophil in the peripheral blood are usually normal. The bone marrow is always hypercellular, with prominent numbers of eosinophils and precursors.

We herein describe a 40-year-old man with FIP1L1/PDGFRA-associated CEL. Regarding the disease, clinical features is upper respiratory infection as initial symptom, and our patient had no history of parasitic infection and allergic disease. The patient presented with splenomegaly, multiple lymph node enlargement, elevated white blood cell and eosinophil count of peripheral blood, and mild anemia. The patient was positive for FIP1L1/PDGFRA. Thus, hypereosinophilic syndrome and reactive eosinophilia can be ruled out in the differential diagnosis of CEL.[12-14] After the diagnosis of CEL associated with FIP1L1/PDGFRA, the patient was treated with Low-dose imatinib. Gene targeting treatment using imatinib led to quick and effective recovery for the patient.

The FIP1L1/PDGFRA fusion gene is the most common clonal genetic abnormality of CEL. Tyrosine kinase inhibitors (TKI), such as imatinib, have been demonstrated to be effective therapies for FIP1L1/PDGFRA-associated CEL, and the FIP1L1- PDGFRA fusion protein is 100 times more sensitive than BCR-ABL1.[15-16] We didn't recognize FIP1L1/PDGFRA-associated CEL and effective therapies to it using imatinib until 2003, and the long-term prognosis of it is still unclear. However, if imatinib treatment is timely and effective, and serious damage of organs such as cardiac damage hasn't yet occurred , the prognosis tends to be favourable. Some patients with CEL may develop imatinib resistance. These patients can choose alternative tyrosine kinase inhibitors such as midostaurin and sorafenib to treat CEL effectively. In the future, whether patients with CEL can safely discontinue imatinib and how to overcome drug resistance for patients with CEL need to be explored.[17-20]

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