

## Case Report

# Chronic eosinophilic leukemia initially presenting with psychotic symptoms: one case report and literature review

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**Abstract:** Chronic eosinophilic leukemia (CEL) is a myeloid malignant proliferative disease with autonomous and clonal proliferation of eosinophilic precursor cells, leading to a persistent increase of eosinophils in the peripheral blood, bone marrow, and surrounding tissues. Along with in-depth research on the pathogenesis and targeted drugs of CEL, imatinib mesylate has been applied in treating CEL. Signs and symptoms of CEL primarily consist of weight loss, cough, fever, malaise, skin and mucosal lesions and diarrhea, etc. Nevertheless, CEL patients presenting with psychotic symptoms as the main manifestations have not been reported. In this article, one case of CEL was manifested with psychotic symptoms. The male patient, 55 years old, was admitted to our hospital due to restlessness and agitation for 3 weeks and increased white blood cell count for 2 weeks. The special clinical manifestations, clinical diagnosis, and treatment process of this patient are summarized, aiming to provide clinical evidence for the diagnosis and therapy of CEL for relevant clinicians.

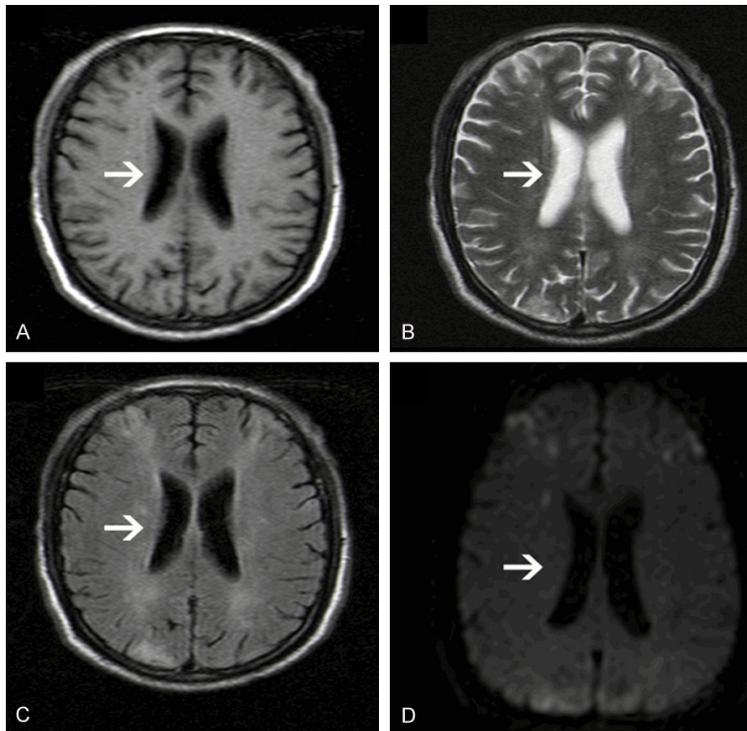
**Keywords:** Chronic eosinophilic leukemia, psychotic symptom, diagnosis, treatment

### Introduction

CEL is a rare myeloproliferative disease characterized by autonomous and clonal proliferation of eosinophilic precursor cells, resulting in a continuous elevation of eosinophils in peripheral blood, bone marrow and surrounding tissues, etc. According to the WHO revised diagnostic criteria of CEL in 2008 [1], CEL can be diagnosed when peripheral blood eosinophils  $\geq 1.5 \times 10^9/L$ , peripheral blood primordial cells  $> 2\%$  or bone marrow primordial cells  $> 5\%$ , accompanied by PDGFR rearrangement, PDGFR rearrangement or FGFR1 rearrangement [1-3]. Otherwise, CEL-NOC or hypereosinophilic syndrome (HES) can be diagnosed. The possibility of other myeloid and lymphocyte-derived malignant diseases accompanied by eosinophilia and PDGFR/FGFR1 gene rearrangement should be eliminated. In this study, one case of CEL manifested with psychotic symptoms is reported, aiming to provide evidence for the diagnosis and treatment of this rare disease.

### Case report

The 55 year old male patient was admitted to our hospital on January 18, 2013 due to restlessness and agitation for 3 weeks and increased white blood cell count for 2 weeks. Prior to admission, the patient suffered from speech disorder, agitation, shouting and screaming, unable to answer questions or accurately recognize family members. He had no significant nausea, vomiting, dizziness and headache, limb movement disorder or obvious abnormality on head CT scan. Upon admission, physical examination revealed restlessness and agitation, unable to cooperate with physical examination, normal body temperature and blood pressure, no pharyngeal congestion, no enlargement of bilateral tonsils, non-palpable superficial lymph nodes, no sternum or abdominal tenderness and non-palpable hepatosplenomegaly. Auxiliary examination: routine blood test: white blood cell (WBC) count =  $24 \times 10^9/L$ , neutrophil percentage = 41.9%, eosinophil per-



**Figure 1.** Multiple spots and patch-like long T1 (A) and T2 (B) signals were observed in bilateral frontotemporal parietal occipital cortex, bilateral radiation coronal region and semi-oval center, showing high signals on water pressure (C) and DWI sequences (D) with explicit boundary.

**Table 1.** Routine biochemical test of the cerebrospinal fluid

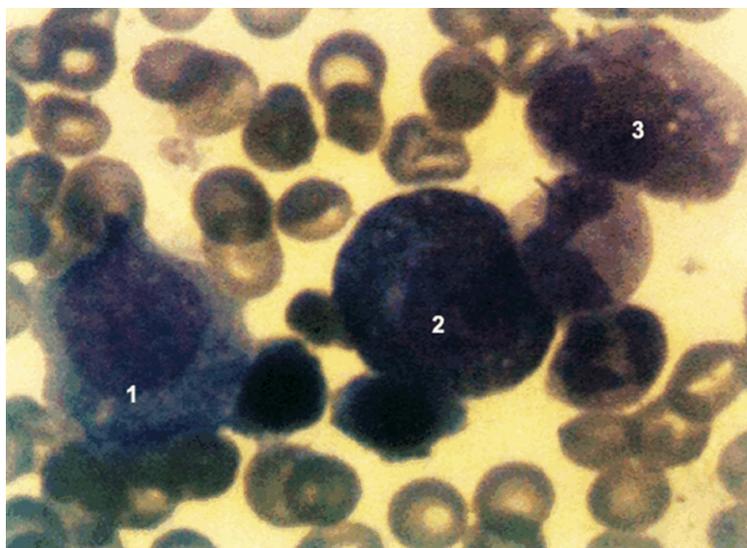
Parameter	Result	Reference value
Appearance	Transparent	
Pandy test	Negative	
Total cell count	10.0	
White blood cell count	3.0	
Glucose level	3.2	
Protein	0.68	
Chloride	125.2	
Adenosine deaminase	0.86	4-20

centage = 38.4%, eosinophil count =  $7.64 \times 10^9/L$ , hemoglobin = 130 g/L, platelet =  $94 \times 10^9/L$ . Serum IgE level was within normal range. Serum *cysticercosis* antibody (-), *toxoplasma gondii* antibody (-), *echinococcosis* (-). No parasite worm eggs were detected in the stool sample. Thyroid function and connective tissue disease-related test and rheumatic immune function tests were normal. Electrocardiogram and cardiac ultrasound were normal. Abdominal ultrasound revealed no significant enlargement

of liver and spleen. Cranial MRI (**Figure 1**) demonstrated multiple hypointense lesions in the brain. The cerebral cortical sulcus was deepened, the cerebral gyrus was narrowed, and the lateral fissure cistern was deepened and widened. Routine biochemical test of cerebrospinal fluid demonstrated that the level of adenosine deaminase was detected as 0.86, significantly lower compared with the normal range (4-20), and no pathological abnormality was detected in the cerebrospinal fluid, as illustrated in **Table 1**. Written informed consent was obtained from this patient.

Bone marrow smear demonstrated that the granulocyte proliferation was active, primitive granulocytes accounted for 5%, 83% for granulocytes, 5% for eosinophilic myelocytes, 4.5% for eosinophilic meta-

myelocytes, 6.5% for eosinophilic stab granulocytes, 19% for eosinophilic segmented granulocytes and 60% for mature eosinophilic granulocytes in the peripheral blood (**Figure 2**). Chromosome karyotype test yielded normal outcomes. BCR/ABL fusion gene (-), FIP1L1-PDGFR $\alpha$  positive (Beijing Hester Clinical Laboratory, China), as demonstrated in **Table 2** and **Figure 3**. RT-PCR of the fusion gene (Institute of Blood Diseases of Peking University People's Hospital, China) reported that FIP1L1-PDGFR $\alpha$  fusion gene was positive, and FIP1L1-PDGFR $\alpha$  (copy number)/ABL (copy number) =  $943/52137 = 1.8\%$ . The patient was clinically diagnosed as chronic eosinophilic leukemia (CEL). Imatinib mesylate (200 mg) was orally administered immediately, and the symptoms of agitation and restlessness were gradually mitigated. After 2-week drug administration, WBC =  $6.4 \times 10^9/L$ , neutrophil percentage = 65%, eosinophil percentage = 4.5%, eosinophil count =  $0.29 \times 10^9/L$ , hemoglobin = 131 g/L, platelet =  $164 \times 10^9/L$ . No morphological and pathological abnormality was detected in the bone marrow after 1-month treatment. The oral dosage of imatinib mesyl-



**Figure 2.** Bone marrow smear test showing the primitive granulocytes (1), eosinophilic promyelocytes (2) and eosinophilic metamyelocytes (3).

**Table 2.** Qualitative detection report of FIP1L1-PDGFR $\alpha$  fusion gene

Parameter	Result
FIP1L1-PDGFR $\alpha$	Positive
Negative control	Negative
Positive control	Positive
Internal control	Positive

ate was reduced to 100 mg. After 3 months, FIP1L1-PDGFR $\alpha$  was negative, and complete hematological remission (CHR) was achieved. After discharge, the patient received routine blood examination and bone marrow puncture in a local hospital, and no abnormality was found. The patient received imatinib mesylate at a dose of 100 mg once a week. No psychotic symptoms recurred. Routine blood test showed WBC and eosinophils were normal. The patient was admitted to our hospital January 18, 2013 and followed up until October 31, 2017.

### Discussion

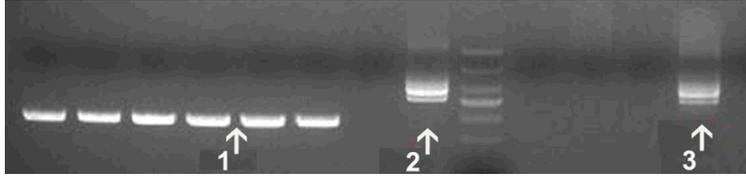
FIP1L1-PDGFR fusion gene has proven to be the most common recurrent molecular genetic abnormality in CEL patients [2]. The molecular genetic basis is the deletion of approximately 800 bases in the middle of 4q12 [del(4)(q12q12)], which leads to the fusion of FIP1L1 gene and PDGFRA gene to form a novel gene FIP1L1/PDGFR $\alpha$  [3]. The genetic product of

PDGFRA is a tyrosine kinase FIP1L1 PDGFRA that is continuously activated, which can express proteins with tyrosine kinase activity and stimulate persistent proliferation of eosinophils. In this report, complete examinations were performed to exclude the possibility of secondary eosinophilia. The results of routine blood test, bone marrow smear and fusion gene detection collectively met the diagnostic criteria of CEL and eventually the patient was diagnosed with CEL. However, the patient initially presented with psychiatric symptoms upon admission, which were not common clinical manifestations of CEL.

Therefore, cranial MRI and lumbar puncture examination were conducted to further exclude the risk of cerebral hemorrhage, central infection and alternative pathological changes.

CEL patients suffer from diverse clinical manifestations ranging from asymptomatic eosinophilia to vital organ failure involved with lung, heart or gastrointestinal tract. These symptoms are mainly caused by the release of eosinophil granule contents, including major basic proteins, eosinophil cationic proteins and eosinophil-derived neurotoxins, which directly damage endothelial cells [4]. In this article, the male CEL patient presented with psychoneurological symptoms as their main clinical manifestations. The symptoms of agitation and restlessness were mitigated after imatinib treatment. At 3 months after discharge, cerebral MRI revealed the severity of hypo-dense lesions was significantly alleviated, indicating that the psychotic symptoms of patients are correlated with CEL. Therefore, extensive attention should be paid to CEL with secondary psychotic symptoms as the first manifestations.

Drug therapy for CEL includes chemical drugs, glucocorticoids, interferons, and tyrosine kinase inhibitors. Except tyrosine kinase inhibitors, the response time of other drug therapies is extremely short and patients fail to obtain molecular remission [5]. FIP1L1-PDGFR $\alpha$  fusion gene, PDGFR $\alpha$  and PDGFR $\beta$  rearrangement



**Figure 3.** Detection of FIP1L1-PDGFR $\alpha$  by RT-PCR. Reference gene (1), positive control (2) and positive FIP1L1-PDGFR $\alpha$ .

gene all have tyrosine kinase activity, which are effective for imatinib mesylate and serve as molecular targeted therapy for CEL [6]. Previous studies [7, 8] have demonstrated that imatinib yields a high therapeutic response rate for CEL with FIP1L1-PDGFR $\alpha$  mutation, but exerts almost no effect on HES without FIP1L1-PDGFR $\alpha$  mutation. The recommended initial dose of imatinib is 100 mg/d, and the maximum dose can reach 400 mg/d [9, 10]. Imatinib can merely inhibit rather than completely eliminate FIP1L1-PDGFR $\alpha$  fusion gene. Interruption of treatment is likely to lead to recurrence. Consequently, extensive attention should be diverted to the maintenance and stability of effective treatment. Metzgeroth et al. [11] applied imatinib to treat 21 CEL patients including 16 cases positive for FIP1L1-PDGFR $\alpha$  and 5 cases positive for PDGFR $\beta$ . The median follow-up time was 26.7 months, 95% of all patients achieved CHR at 3 months after treatment and 87% obtained molecular remission at 1 year following treatment. Patients receiving maintenance treatment did not recur. As Klion et al. reported [12], 5 CEL patients who were relieved after oral administration of 300-400 mg/d imatinib received maintenance treatment for at least 6 months with 10-100 mg/d dose reduction every 3 months. The treatment was terminated if the patients did not recur. All 5 patients suffered from molecular recurrence and obtained molecular remission after treatment with imatinib. Helbig et al. [13] reported that 7 CEL cases obtained remission after imatinib treatment, followed by maintenance therapy at a dose of 100-200 mg/w. The median follow-up time was 30 months. All 7 patients maintained CHR and molecular remission, suggesting that a single dose of imatinib weekly can serve as the maintenance therapy of CEL.

In this report, the patient was treated with the initial dose of imatinib mesylate (200 mg/d), and then the clinical symptoms were absent, the routine blood test and bone marrow smear

yielded normal results, indicating the high clinical efficacy of imatinib mesylate for this case. The dose of imatinib mesylate was reduced to 100 mg/d after CHR. Reexamination demonstrated that the patient was negative for FIP1L1/PDGFR fusion gene, indicating that molecular remission was achieved.

The patient continued to orally receive low-dose FIP1L1/PDGFR $\alpha$  (100 mg/w) as a maintenance therapy. The patient did not recur until the final follow-up visit (October 31, 2017). The psychotic symptoms emerged as the first symptoms in this CEL case. After oral administration of imatinib mesylate, the psychotic symptoms were gradually eased accompanied with the decrease of leukocytes and eosinophils. The diagnosis and treatment of this CEL patient indicates that imatinib mesylate is an efficacious treatment of CEL with positive FIP1L1-PDGFR $\alpha$  fusion gene, which can facilitate CEL patients to obtain molecular remission treated with small-dose maintenance therapy.

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### Disclosure of conflict of interest

None.

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