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**Eighty-year-old man with rare chronic neutrophilic leukemia caused by *CSF3R* T618I mutation: A case report and review of literature**

Li YP *et al*. Old man with rare chronic neutrophilic leukemia

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**Author contributions:** Li YP was directly involved in the diagnosis and treatment of the disease and follow-up observation, recorded the clinical characteristics of the patient, followed the results of gene sequencing and laboratory tests, and drafted and revised the manuscript; Chen N assessed the academic and practical value of the case, analyzed the gene sequencing results and the laboratory testing results, collected image data, and revised the manuscript; Ye XM tracked the results of gene sequencing and laboratory tests, and collected the images and other information; Xia YS controlled and adjusted the treatment plan of this case, organized the consultation of specialists, was directly involved in the diagnosis and treatment of the disease and follow-up observation, and participated in the writing and modification of the article.

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**Abstract**

BACKGROUND

Chronic neutrophilic leukemia (CNL) is a rare bone marrow proliferative tumor and a heterogeneous disorder. In 2016, the World Health Organization included activating mutations in the *CSF3R* gene as one of the diagnostic criteria, with *CSF3R* T618I being the most common mutation. The disease is often accompanied by splenomegaly, but no developmental abnormalities and significant reticular fibrosis, and no Ph chromosome and *BCR-ABL* fusion gene. So, it is difficult to diagnose at the first presentation in the absence of classical symptoms. Herein we describe a rare CNL patient without splenomegaly whose initial diagnostic clue was neutrophilic hyperactivity.

CASE SUMMARY

The patient is an 80-year-old Han Chinese man who presented with one month of fatigue and fatigue aggravation in the last half of the month. He had no splenomegaly, but had persistent hypofibrinogenemia, obvious skin bleeding, and hemoptysis, and required repeated infusion of fibrinogen therapy. After many relevant laboratory examinations, histopathological examination, and sequencing analysis, the patient was finally diagnosed with CNL [*CSF3R* T618I positive: c.1853C>T (p.T618I) and c.2514T>A (p.C838)].

CONCLUSION

The physical examination and blood test for tumor-related genes are insufficient to establish a diagnosis of CNL. Splenomegaly is not that important, but hyperplasia of interstitial neutrophil system and activating mutations in *CSF3R* are important clues to CNL diagnosis.

**Key Words:** Chronic neutrophilic leukemia; Leukemia; Hyperplasia of interstitial neutrophil system; *CSF3R*; Case report; Hydroxyurea; Allopurinol

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**Core Tip:** An 80-year-old man had a long history of interstitial pneumonia. His leukocyte levels were extremely high, while the fibrinogen and prothrombin activities were low. His urea, uric acid, and creatinine values were high, and there were reticulated fibers around the blood vessels, and bone marrow fibrosis was obvious. His granulocyte system was extremely hyperplastic. Importantly, our gene mutation test found that the *CSF3R* gene was mutated. Therefore, we eventually diagnosed his symptoms as chronic neutrophilic leukemia (CNL). The particularity of the case lies in that CNL is often accompanied by splenomegaly, but the patient had no splenomegaly.

**INTRODUCTION**

Chronic neutrophilic leukemia (CNL) is an extremely rare myeloproliferative neoplasm (MPN)[1]. It is a heterogeneous disease, clinically characterized by the continuous increase of mature neutrophils, which could be attributed to *CSF3R* mutations, with peripheral blood accompanied by little or no naive granulocytes, monocytes, and basophils[2]. There is usually splenomegaly and hyperplasia of bone marrow granulocytes, the disease is not accompanied by dysplasia and significant reticular fibrosis, and there is no Ph chromosome or *BCR/ABL* fusion gene[3]. The incidence of the disease is low, and it is easy to be misdiagnosed and missed.

**CASE PRESENTATION**

***Chief complaints***

One month of fatigue and fatigue aggravation in the last half of the month.

***History of present illness***

The patient is an 80-year-old Han Chinese man who presented with fatigue and fatigue aggravation for half of the month (August 2019-October 2019).

***History of past illness***

The patient had a history of interstitial pneumonia for5 years. He denied a history of chronic diseases such as diabetes, hypertension, or heart disease. He denied any history of infection such as tuberculosis and hepatitis. He denied any drug allergies. He had no smoking or drinking history.

***Personal and family history***

There was no family history of systemic autoimmune disease, cardiovascular disease, coagulation dysfunction, or malignancy, and any other family history.

***Physical examination***

The patient’s vital signs were stable and normal (temperature: 36.5 °C; pulse rate: 76/min; respiration rate: 19 breaths/min; blood pressure: 130/80 mmHg). Lung auscultation demonstrated heavy breath sounds and a small amount of wet and dry rales can be heard. Liver, spleen, and kidney examinations showed no obvious abnormalities. The patient was characterized by mild anemia with large ecchymosis on the outside of the left thigh, and the sternal tenderness was positive.

***Laboratory examinations***

The laboratory findings were as follows: Platelet count was 102 × 109/L, leucocyte count was 324.06 × 109/L, neutrophil count was 285.38 × 109/L, and hemoglobin concentration was 100 g/L. Regarding coagulation function, the patient’s fibrinogen was 0.6 g/L (normal value: 2-4 g/L), and prothrombin activity was 46.1% (normal value: 80-120 g/L). His procalcitonin was 0.701 ng/mL. The five tests of respiratory tract infection pathogen antibody were all negative. The renal function indexes were as follows: UREA was 9.7 mmol/L; creatinine was 169.3 μmol/L; and uric acid was 844 μmol/L. with regard to routine urine examination, his occult blood was 1 + Ca25Ery/μL, urine protein was 1 + 0.3 g/L, and ferroprotein was greater than 1650 ng/mL. The autoantibodies and anti-neutrophil PMN antibodies were negative. Constant element, G/GM test, and fecal examination were all normal.

***Imaging examinations***

The result of blood film test was that more than 80% were neutral rod-shaped nuclei and neutral lobulated nuclear granulocytes (Figure 1). Naive cells (promyelocytes, myelocytes, and metamyelocytes) were less than 10%. No primitive granulocytes were seen, and no granulocytes were abnormally developed.

The bone marrow report was as follows: Myeloproliferation was extremely active (Figure 2). The interstitial neutrophil system was extremely proliferative, mainly mesenchymal and below-stage cells, and there was no increase in eosinophils. Bone marrow erythroids were rare, and megakaryocytes had not increased.

Comori staining showed that the reticular fibers were positive; bone marrow fibrosis was classified as MF-1.

***Karyotype analysis***

No abnormal karyotype.

***Blood tumor-related gene examination***

The *CSF3R* mutations in patients were determined by Beijing Hester Medical Laboratory Co. LTD (Beijing, China). *BCR*/*ABL*-190, -210, and -230 fusion genes were all negative. *PML*/*RARa* and *S*/*V* fusion genes were all negative. No MPN-related gene mutations were detected: *W515L* mutant, *W515K* mutant, *JAK2*/*V617F* mutant, *CALR* gene exon 9, *PDGFRB*, *PDGFRA*, *FIPIL1*/*PDGFRα*, and *JAK2* gene exon 12 were all negative. More importantly, the key to this diagnosis was that we found a *CSF3R* T618I mutation. The details of the three *CSF3R* mutations are shown in Figure 3A-C and Table 1.

***Differential diagnosis***

CNL is a rare *BCR*/*ABL*-negative myeloproliferative tumor. In 2013, it was discovered that the *CSF3R* T618I mutation is a highly specific and sensitive molecular diagnostic marker of CNL. In 2016, the World Health Organization (WHO) identified *CSF3R* mutation as a CNL diagnostic marker. In the present case, we detected a c.1853C>T (p.T618I) mutation (heterozygous). According to the current literature, this is a specific mutation of CNL and atypical chronic myelocytic leukemia (aCML), and it is a pathological mutation[4]. Furthermore, the patient’s peripheral blood leukocyte count was 324.06 × 109/L (> 25 × 109/L), the neutral lobulated nuclei and rods were more than 80%, immature cells (promyeloid, medium, and late granulocytes) were less than 10%, and there were no primordial granulocytes and no granulocytes dysplasia. The myeloid hyperplasia was hyperactive, the granulocyte system in the stroma was hyperproliferating, mainly the cells in the middle and young granulocytes and the following stages, and megakaryocytes were not increased. All the fusion genes of *BCR*/*ABL*-190, -210, and -230 were negative. No MPN-related mutations were detected. Pointing away from CNL is absence of hepatosplenomegaly and this patient also had a c.1260T>C (p.T420T) mutation (no pathogenicity) and a c.2514 T>A (p.C838) mutation (the mutation results in a frame shift and premature termination of the amino acid coding). In addition, the patient had persistent low fibrinogenemia, obvious skin bleeding, and hemoptysis.

**FINAL DIAGNOSIS**

The patient was diagnosed with chronic neutrophil leukemia, hypofibrinogenemia, uric acid nephropathy, and interstitial pneumonia.

**TREATMENT**

The patient received hydroxymethylnicotinamide tablets, sodium bicarbonate tablets, and allopurinol tablets. Oral administration of hydroxymethylnicotinamide tablets was given to lower cells with fluid replacement, and sodium bicarbonate tablets combined with allopurinol tablets were prescribed to alkalinize urine.

The patient had obvious bleeding symptoms such as skin bleeding and hemoptysis, and these symptoms were relieved after fibrinogen supplementation and cryoprecipitation treatment. This patient had severe pulmonary infection with type Ι respiratory failure during treatment, and the symptoms improved after anti-infection and hormone therapy.

When the patient was discharged, the blood leukocytes dropped to normal levels, the kidney function was normal, and fibrinogen was normal. The bleeding symptoms and the lung infection were controlled.

The patient was intermittently treated with hydroxyurea (0.5 g, oral, 1-2 times/d) for maintenance treatment after discharge from hospital. The blood routine was reviewed weekly, and the dosage of the drug was adjusted according to the routine blood results.

**OUTCOME AND FOLLOW-UP**

We followed the patient for 3 mo, and 3 mo after discharge, the patient died because of a lung infection.

**DISCUSSION**

CNL is a clinically rare hematological tumor. It was first reported by Tuohy[5] in 1920. In 2001, WHO confirmed its diagnostic classification and classified it as a myeloproliferative tumor[6]. In 2008, the WHO revised the disease diagnostic criteria (as mentioned above)[7]. Large-scale epidemiological studies on the disease are lacking. According to comprehensive literature case reports, the incidence rate among the elderly is high, which is consistent with the present report (the patient was 80 years old)[8]. More men than women have a poor prognosis, with a median survival time of 23.5 mo[9].

Fatigue is the most common symptom at the initial diagnosis of this disease[10]. In this report, the patient had obvious fatigue and had extreme fatigue for half a month. Other symptoms include weight loss, skin ecchymosis, abdominal distension, anorexia, and night sweats[11]. Similarly, a large ecchymosis can be seen on the lateral side of his left thigh. Lymphadenopathy and hepatomegaly are not common[12]. Hepatosplenomegaly, one of the main features of CNL, is a key indicator to distinguish leukemoid reaction from CNL[13,14]. Most patients with CNL have hepatosplenomegaly at the time of diagnosis, but hepatosplenomegaly is not common in the pathological manifestations of leukemoid reaction. Furthermore, leukemoid reaction is a leukemia-like blood reaction that the body is stimulated by certain diseases or external factors, among which neutrophil type is the most common. Patients with leukemoid reaction have no hepatomegaly or splenomegaly, the total number of white blood cells in the patients can reach 50 × 109/L, and the total number of myeloblasts, primitive cells, and young granulocytes increases[15]. In the present report, the number of white blood cells of the patient was increased to 324.06 × 109/L, and the young granulocytes also increased. Most unusually, no splenomegaly can be seen, which greatly increased the probability of misdiagnosis of CNL. It suggests that the characteristics of splenomegaly might need careful consideration to avoid misdiagnosis.

The unexplained rise of leukocytes and mature neutrophils is a key characteristic of this disease[16]. It should be noted that the increase of CNL leukocytes is not accompanied by the increase of monocytes, eosinophils, and basophils, abnormal development of granulocytes, or a significant increase in naive granulocytes[17]. The patient in this report had fatigue at the first diagnosis, the leukocytes were significantly increased, and infections and tumors were excluded. More than 80% of mature granulocytes were immature granulocytes and monocytes. Judging from the 2008 WHO diagnostic criteria, five of the eight diagnostic criteria belong to the excluded diagnosis. We performed a CML fusion gene or chromosome examination at the time of diagnosis, excluding CML diagnosis[18]. The patient had no elevated eosinophils. We also tested for *W515L*, *W515K*, *JAK2/V617F*, exon 9 of *CALR*, *PDGFRB*, *PDGFRA*, *FIPIL1/PDGFRα*, and *JAK2* genes related to MPN tumors, which ruled out this type of disease[19-21]. The patient had mildly reduced hemoglobin and normal range platelet count (102 × 109/L), but on the low side. Combined with bone marrow examination, MPN can be excluded. CNL is similar to aCML and chronic myelomonocytic leukemia (CMML) in clinical manifestations, cytogenetics, and molecular biology[18]. Special attention should be paid to the diagnosis of CNL. Peripheral blood naive granulocyte ratio in aCML patients is greater than 10%, while peripheral blood mononuclear cells in CMML patients continue to be greater than 1 × 109/L. Moreover, the changes in the number of mononuclear cells in the bone marrow can be used to identify aCML and CMML[18,22]. In the present report, the case had a less than 10% blood naive granulocytes ratio (including early, medium, and late cells) and had a normal ratio of peripheral blood mononuclear cells.

In early 2013, Maxson *et al*[23]and Pardanani *et al*[24] discovered a *CSF3R* mutation, which has milestone significance for the diagnosis of CNL. *CSF3R* mutation confirmed the presence of myeloid clones and ruled out other blood tumors. The *CSF3R* mutation occurred in more than 90% of patients who met the 2008 WHO diagnostic criteria for CNL. The *CSF3R* mutation determined the WHO diagnostic criteria for CNL at the molecular level. Two types of mutations were found in *CSF3R*: *CSF3R* T618I and *CSF3R* T615A[23,25], which result in differential sensitivity to inhibition of tyrosine kinases downstream of *CSF3R*. CSF3R is a member of the hematopoietic cell receptor superfamily. It is located on chromosome 1p34.3 and has the functions of promoting the proliferation, survival, and differentiation of neutrophils. Although CSF3R itself has no endogenous tyrosine kinase activity, it can change its conformation through ligand binding to stimulate a variety of tyrosine kinases related to its cell activity range, including JAKs, SRC kinase family, and tyrosine kinase. And important signaling pathways involved include STAT, PI3K-AKT, and RAS-MAPK[11,24,26], showing that its mechanism of action is very complicated. As the latest research results, mutations of *CSF3R* are related to many diseases, most of which are related to myeloid system diseases, such as hereditary neutropenia (severe congenital neutropenia), myelodysplastic syndrome, AML, and CNL[26]. T618I is the most frequent mutation[24], and *CSF3R* mutations were also detected in our patient, including *CSF3R* T618I mutation, T420T synonymous mutation, and C838 mutation. It has been reported that *JAK2*/*V617F* mutation has been detected in a small number of diagnosed CNL patients, but the incidence is low and the specificity is poor[27]. The mutations in the *JAK2*/*V617F* gene and exon 12 of *JAK2* gene were undetectable in our patient.

Plasma fibrinogen is mainly used as a diagnostic indicator for coagulation diseases. Recent studies have found that plasma fibrinogen levels in patients with various malignant tumors are significantly elevated, and are closely related to the occurrence and development, recurrence, and metastasis of malignant tumors[28]. However, the characteristics of hypofibrinogenemia appeared in the present case, which is difficult to explain. Although reports on the characteristics of hypofibrinogenemia in CNL patients are extremely rare, this deserves the attention of clinicians.

The current commonly used treatment methods for CNL include hydroxycarbamide, interferon-alpha, and induction chemotherapy, which can alleviate the symptoms of CNL, but there is no significant improvement to the survival of CNL patients[20,29,30]. Allogeneic hematopoietic stem cell transplantation is considered an effective method for curing the disease, but the incidence of transplant-related death and transplant-related complications is high[31]. In the present case, after oral administration with the nucleotide reductase inhibitor hydroxycarbamide, the number of leukocytes dropped to normal levels. After discharge, hydroxycarbamide was used intermittently for maintenance therapy. Routine blood test was reviewed weekly, and drug dosage was adjusted according to routine blood test results.

With the disclosure of *CSF3R* gene mutation, CNL targeted therapy was born. The JAK1/2 inhibitor ruxolitinib was used to treat a CNL patient with *CSF3R* T618I mutation[32,33], and achieved a dose-dependent clinical effect. At present, the diagnosis and treatment of CNL in China are still a problem. With the popularization of *CSF3R* mutation gene detection and the application of targeted drugs, the diagnosis of CNL will be clearer and the prognosis will be improved.

**CONCLUSION**

CNL treatment is still a great challenge for clinicians. The regular features are insufficient for the diagnosis of CNL. In this case, the patient had combined multiple diseases. Therefore, early genetic screening, multidirectional drug treatment, and comprehensive consideration of the treatment effect are necessary means of prevention and diagnosis. Targeted therapy for *CSF3R* will be more beneficial to the clinical individualized treatment and accurate prognosis assessment.

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**Footnotes**

**Informed consent statement:** The patient provided informed written for publication of this case report and accompanying images.

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**CARE Checklist (2016) statement:** The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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**Figure Legends**



**Figure 1 Histology of blood**. Peripheral blood smear (Wright-Giemsa staining, × 500).



**Figure 2 Histology of bone marrow biopsy**. Bone marrow aspirate smear showing granulocytic proliferation, many mature neutrophils with toxic changes, and no increased blasts (Wright-Giemsa staining, × 500).



**Figure 3 Sequencing of mutant sites**. A: c.1260T>C (p.T420T) mutation; B: c.1853C>T (p.T618I) mutation; C: c.2514T>A (p.C838) mutation.

**Table 1 Analysis of *CSF3R* gene mutations**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Testing content** | **Exons 1-17 of *CSF3R*** |  |  |  |  |
| **Method** | **PCR & gene sequencing**  |  |  |  |  |
|  | Gene | Exon  | Variation type | Variation point | Remarks |
| Results | *CSF3R* (NM\_156039) | 1 | None | None | None |
| 2 | None | None | None |
| 3 | None | None | None |
| 4 | None | None | None |
| 5 | None | None | None |
| 6 | None | None | None |
| 7 | None | None | None |
| 8 | None | None | None |
| 9 | None | None | None |
| 10 | Synonymous mutation | c.1260T>C (p.T420T) | This mutation leads to premature termination of peptide synthesis |
| 11 | None | None | None |
| 12 | None | None | None |
| 13 | None | None | None |
| 14 | Missense mutation | c.1853C>T (p.T618I) | This is a specific mutation of CNL and aCML, and it is a pathological mutation  |
| 15 | None | None | None |
| 16 | None | None | None |
| 17 | Nonsense mutation | c.2514T>A (p.C838) | This mutation leads to protein premature termination |

CNL: Chronic neutrophilic leukemia; aCML: Atypical chronic myelocytic leukemia.