

# World Journal of *Clinical Cases*

*World J Clin Cases* 2020 December 26; 8(24): 6213-6545



## MINIREVIEWS

- 6213 Role of gut microbiome in regulating the effectiveness of metformin in reducing colorectal cancer in type 2 diabetes

*Huang QY, Yao F, Zhou CR, Huang XY, Wang Q, Long H, Wu QM*

## ORIGINAL ARTICLE

## Retrospective Cohort Study

- 6229 Impact factors of lymph node retrieval on survival in locally advanced rectal cancer with neoadjuvant therapy

*Mei SW, Liu Z, Wang Z, Pei W, Wei FZ, Chen JN, Wang ZJ, Shen HY, Li J, Zhao FQ, Wang XS, Liu Q*

## Retrospective Study

- 6243 Three-year follow-up of Coats disease treated with conbercept and 532-nm laser photocoagulation

*Jiang L, Qin B, Luo XL, Cao H, Deng TM, Yang MM, Meng T, Yang HQ*

- 6252 Virus load and virus shedding of SARS-CoV-2 and their impact on patient outcomes

*Chen PF, Yu XX, Liu YP, Ren D, Shen M, Huang BS, Gao JL, Huang ZY, Wu M, Wang WY, Chen L, Shi X, Wang ZQ, Liu YX, Liu L, Liu Y*

- 6264 Risk factors for *de novo* hepatitis B during solid cancer treatment

*Sugimoto R, Furukawa M, Senju T, Aratake Y, Shimokawa M, Tanaka Y, Inada H, Noguchi T, Lee L, Miki M, Maruyama Y, Hashimoto R, Hisano T*

- 6274 Cause analysis and reoperation effect of failure and recurrence after epiblepharon correction in children

*Wang Y, Zhang Y, Tian N*

## Clinical Trials Study

- 6282 Effects of different acupuncture methods combined with routine rehabilitation on gait of stroke patients

*Lou YT, Yang JJ, Ma YF, Zhen XC*

## Observational Study

- 6296 Application of endoscopic submucosal dissection in duodenal space-occupying lesions

*Li XY, Ji KY, Qu YH, Zheng JJ, Guo YJ, Zhang CP, Zhang KP*

- 6306 Early renal injury indicators can help evaluate renal injury in patients with chronic hepatitis B with long-term nucleos(t)ide therapy

*Ji TT, Tan N, Lu HY, Xu XY, Yu YY*

**Prospective Study**

- 6315** Neoadjuvant chemoradiotherapy plus surgery in the treatment of potentially resectable thoracic esophageal squamous cell carcinoma  
*Yan MH, Hou XB, Cai BN, Qu BL, Dai XK, Liu F*

**CASE REPORT**

- 6322** Uterine rupture in patients with a history of multiple curettages: Two case reports  
*Deng MF, Zhang XD, Zhang QF, Liu J*
- 6330** Pleural effusion and ascites in extrarenal lymphangiectasia caused by post-biopsy hematoma: A case report  
*Lin QZ, Wang HE, Wei D, Bao YF, Li H, Wang T*
- 6337** Eighty-year-old man with rare chronic neutrophilic leukemia caused by CSF3R T618I mutation: A case report and review of literature  
*Li YP, Chen N, Ye XM, Xia YS*
- 6346** Sigmoid colon duplication with ectopic immature renal tissue in an adult: A case report  
*Namgung H*
- 6353** Paraplegia from spinal intramedullary tuberculosis: A case report  
*Qu LM, Wu D, Guo L, Yu JL*
- 6358** Confocal laser endomicroscopy distinguishing benign and malignant gallbladder polyps during choledochoscopic gallbladder-preserving polypectomy: A case report  
*Tang BF, Dang T, Wang QH, Chang ZH, Han WJ*
- 6364** Sclerosing stromal tumor of the ovary with masculinization, Meig's syndrome and CA125 elevation in an adolescent girl: A case report  
*Chen Q, Chen YH, Tang HY, Shen YM, Tan X*
- 6373** Primary pulmonary malignant melanoma diagnosed with percutaneous biopsy tissue: A case report  
*Xi JM, Wen H, Yan XB, Huang J*
- 6380** SRY-negative 45,X/46,XY adult male with complete masculinization and infertility: A case report and review of literature  
*Wu YH, Sun KN, Bao H, Chen YJ*
- 6389** Refractory case of ulcerative colitis with idiopathic thrombocytopenic purpura successfully treated by Janus kinase inhibitor tofacitinib: A case report  
*Komeda Y, Sakurai T, Sakai K, Morita Y, Hashimoto A, Nagai T, Hagiwara S, Matsumura I, Nishio K, Kudo M*
- 6396** Immunotherapies application in active stage of systemic lupus erythematosus in pregnancy: A case report and review of literature  
*Xiong ZH, Cao XS, Guan HL, Zheng HL*

- 6408** Minimally invasive maxillary sinus augmentation with simultaneous implantation on an elderly patient: A case report  
*Yang S, Yu W, Zhang J, Zhou Z, Meng F, Wang J, Shi R, Zhou YM, Zhao J*
- 6418** Congenital nephrogenic diabetes insipidus due to the mutation in *AVPR2* (c.541C>T) in a neonate: A case report  
*Lin FT, Li J, Xu BL, Yang XX, Wang F*
- 6425** Primary gastric melanoma in a young woman: A case report  
*Long GJ, Ou WT, Lin L, Zhou CJ*
- 6432** Extreme venous letting and cupping resulting in life-threatening anemia and acute myocardial infarction: A case report  
*Jang AY, Suh SY*
- 6437** Novel conservative treatment for peritoneal dialysis-related hydrothorax: Two case reports  
*Dai BB, Lin BD, Yang LY, Wan JX, Pan YB*
- 6444** Clinical characteristics of pulmonary cryptococcosis coexisting with lung adenocarcinoma: Three case reports  
*Zheng GX, Tang HJ, Huang ZP, Pan HL, Wei HY, Bai J*
- 6450** Fracture of the scapular neck combined with rotator cuff tear: A case report  
*Chen L, Liu CL, Wu P*
- 6456** Synchronous colonic mucosa-associated lymphoid tissue lymphoma found after surgery for adenocarcinoma: A case report and review of literature  
*Li JJ, Chen BC, Dong J, Chen Y, Chen YW*
- 6465** Novel mutation in the *ASXL3* gene in a Chinese boy with microcephaly and speech impairment: A case report  
*Li JR, Huang Z, Lu Y, Ji QY, Jiang MY, Yang F*
- 6473** Recurrent thrombosis in the lower extremities after thrombectomy in a patient with polycythemia vera: A case report  
*Jiang BP, Cheng GB, Hu Q, Wu JW, Li XY, Liao S, Wu SY, Lu W*
- 6480** Status epilepticus as an initial manifestation of hepatic encephalopathy: A case report  
*Cui B, Wei L, Sun LY, Qu W, Zeng ZG, Liu Y, Zhu ZJ*
- 6487** Delayed diagnosis of prosopagnosia following a hemorrhagic stroke in an elderly man: A case report  
*Yuan Y, Huang F, Gao ZH, Cai WC, Xiao JX, Yang YE, Zhu PL*
- 6499** Oral myiasis after cerebral infarction in an elderly male patient from southern China: A case report  
*Zhang TZ, Jiang Y, Luo XT, Ling R, Wang JW*
- 6504** Rare case of drain-site hernia after laparoscopic surgery and a novel strategy of prevention: A case report  
*Gao X, Chen Q, Wang C, Yu YY, Yang L, Zhou ZG*

- 6511** Extracorporeal shock wave therapy treatment of painful hematoma in the calf: A case report  
*Jung JW, Kim HS, Yang JH, Lee KH, Park SB*
- 6517** Takotsubo cardiomyopathy associated with bronchoscopic operation: A case report  
*Wu BF, Shi JR, Zheng LR*
- 6524** Idiopathic adulthood ductopenia with elevated transaminase only: A case report  
*Zhang XC, Wang D, Li X, Hu YL, Wang C*
- 6529** Successful endovascular treatment with long-term antibiotic therapy for infectious pseudoaneurysm due to *Klebsiella pneumoniae*: A case report  
*Wang TH, Zhao JC, Huang B, Wang JR, Yuan D*
- 6537** Primary duodenal tuberculosis misdiagnosed as tumor by imaging examination: A case report  
*Zhang Y, Shi XJ, Zhang XC, Zhao XJ, Li JX, Wang LH, Xie CE, Liu YY, Wang YL*

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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

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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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interest.

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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.

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## INTRODUCTION

Chronic neutrophilic leukemia (CNL) is an extremely rare myeloproliferative neoplasm (MPN)<sup>[1]</sup>. 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<sup>[2]</sup>. 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<sup>[3]</sup>. 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 for 5 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  $102 \times 10^9/L$ , leucocyte count was  $324.06 \times 10^9/L$ , neutrophil count was  $285.38 \times 10^9/L$ , 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  $\mu$ mol/L; and uric acid was 844  $\mu$ mol/L. With regard to routine urine examination, his occult blood was 1 + Ca25Ery/ $\mu$ L, 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/RAR $\alpha$*  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*, *FIP1L1/PDGFR $\alpha$* , 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-3C 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<sup>[4]</sup>. Furthermore, the patient's peripheral blood leukocyte count was  $324.06 \times 10^9/L$  ( $> 25 \times 10^9/L$ ), 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.

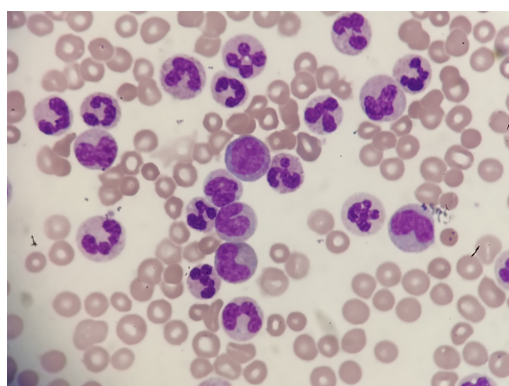
## FINAL DIAGNOSIS

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

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

Testing content	Exons 1-17 of <i>CSF3R</i>				
Method	PCR & gene sequencing				
	Gene	Exon	Variation type	Variation point	Remarks
Results	<i>CSF3R</i> (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

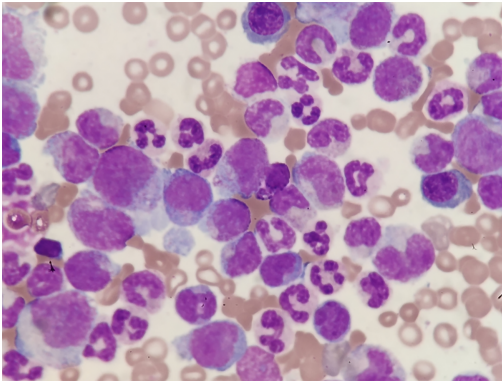
CNL: Chronic neutrophilic leukemia; aCML: Atypical chronic myelocytic leukemia.

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

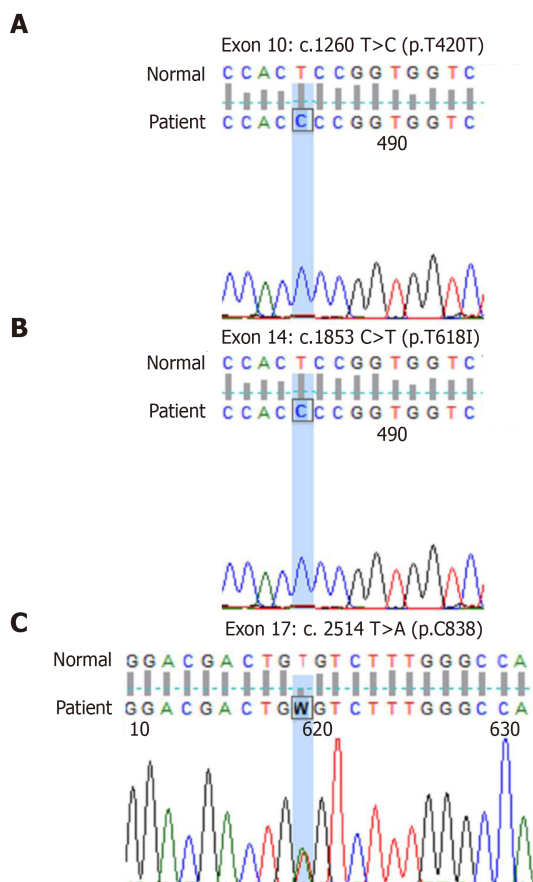
## TREATMENT

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



**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,  $\times 500$ ).



**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.

cryoprecipitation treatment. This patient had severe pulmonary infection with type I 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<sup>[5]</sup> in 1920. In 2001, WHO confirmed its diagnostic classification and classified it as a myeloproliferative tumor<sup>[6]</sup>. In 2008, the WHO revised the disease diagnostic criteria (as mentioned above)<sup>[7]</sup>. 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)<sup>[8]</sup>. More men than women have a poor prognosis, with a median survival time of 23.5 mo<sup>[9]</sup>.

Fatigue is the most common symptom at the initial diagnosis of this disease<sup>[10]</sup>. 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<sup>[11]</sup>. Similarly, a large ecchymosis can be seen on the lateral side of his left thigh. Lymphadenopathy and hepatomegaly are not common<sup>[12]</sup>. Hepatosplenomegaly, one of the main features of CNL, is a key indicator to distinguish leukemoid reaction from CNL<sup>[13,14]</sup>. 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  $50 \times 10^9/L$ , and the total number of myeloblasts, primitive cells, and young granulocytes increases<sup>[15]</sup>. In the present report, the number of white blood cells of the patient was increased to  $324.06 \times 10^9/L$ , 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<sup>[16]</sup>. 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<sup>[17]</sup>. 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<sup>[18]</sup>. The patient had no elevated eosinophils. We also tested for *W515L*, *W515K*, *JAK2/V617F*, exon 9 of *CALR*, *PDGFRB*, *PDGFRA*, *FIP1L1/PDGFRa*, and *JAK2* genes related to MPN tumors, which ruled out this type of disease<sup>[19-21]</sup>. The patient had mildly reduced hemoglobin and normal range platelet count ( $102 \times 10^9/L$ ), 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<sup>[18]</sup>. 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  $1 \times 10^9/L$ . Moreover, the changes in the number of mononuclear cells in the bone marrow can be used to identify aCML and CMML<sup>[18,22]</sup>. 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*<sup>[23]</sup> and Pardananani *et al*<sup>[24]</sup> 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<sup>[23,25]</sup>, 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<sup>[11,24,26]</sup>, 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<sup>[26]</sup>. T618I is the most frequent mutation<sup>[24]</sup>, 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<sup>[27]</sup>. 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<sup>[28]</sup>. 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<sup>[20,29,30]</sup>. 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<sup>[31]</sup>. 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<sup>[32,33]</sup>, 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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