Clinical Case Report

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ELANE gene mutation-induced cyclic neutropenia manifesting as recurrent fever with oral mucosal ulcer

A case report

Xin Chen, MS, Wansheng Peng, MS, Zhen Zhang, MS, Yumeng Wu, MS, Jiali Xu, MS*, Yan Zhou, BS, Li Chen, BS

Abstract

Background: Cyclic neutropenia (CyN) is a rare hematological disease. Herein, a CyN girl, aged 3 years and 2 months, with recurrent fever and oral mucosal ulcer caused by neutrophil elastase (ELANE) gene mutation is reported.

Case presentation: A 3 years and 2 months old girl presented with recurrent fever and oral mucosal ulcer for 1 year. Routine blood test revealed that her absolute neutrophil count repeatedly decreased (minimum 0. 04×10^9/L) every 21 days on an average. Gene testing showed that the patient suffered from ELANE gene heterozygous mutation (c.197T>G) (exon2) (p.M66R). She was finally diagnosed as CyN. The patient's symptoms were relieved after infection prevention and treatment as well as granulocyte-colony stimulating factor (G-CSF) therapy. Her condition continues to remain stable.

Conclusion: Active prevention and treatment of infection as well as G-CSF therapy can successfully control CyN.

Abbreviations: CyN = cyclic neutropenia, ELANE = neutrophil elastase, G-CSF = granulocyte-colony stimulating factor, HSCT = hematopoietic stem cell transplantation, SCN = severe congenital neutropenia.

Keywords: cyclic neutropenia, *ELANE* gene, fever, G-CSF, oral mucosal ulcer

1. Introduction

CyN is a rare hematological disease caused by gene mutations. The main clinical manifestations are recurrent fever, oral mucosal ulcer, lung infection and periodic decrease of peripheral blood ANC (ANC is often $<0.2 \times 10^9$/L and lasts 3–5 days), with an average period of 21 days.[1] CyN cases diagnosed by gene testing are being increasingly reported in foreign countries,[2,3] but not in China. Herein, we reported a girl, aged 3 years and 2 months, who developed CyN caused by ELANE gene mutation that manifested as recurrent fever with oral mucosal ulcer. The disease was well controlled after prevention and treatment of infection as well as G-CSF therapy.

2. Case presentation

This case report was approved by the Ethics Committee of The First Affiliated Hospital of Bengbu Medical College, and informed consent was obtained from the guardian of the patient.

The patient was a girl, aged 3 years and 2 months. She visited the Pediatric Emergency Department of the First Affiliated Hospital of Bengbu Medical College on January 2, 2017, due to fever and oral mucosal ulcer. One day before admission, the patient developed fever and the body temperature was up to 39.5°C, accompanied by oral ulcers and sore throat. After oral administration of paracetamol, the body temperature dropped to 38°C, but she felt weak, and was admitted to the Pediatric Emergency Department of our hospital. Routine blood test revealed WBC 5.09×10^9/L and ANC 0.05×10^9/L, and she was diagnosed as neutropenia. In terms of disease history, the patient had come in contact with flu patients 5 days ago. In the past year, she was admitted to hospitals 14 times due to fever and oral mucosal ulcer, and was found to have low ANC ($0.04–0.18 \times 10^9$/L) each time. She was discharged after 5–7 days of anti-infective and G-CSF treatment. The patient was G1P1, of Han nationality, full-term normal delivery, with a birth weight 3.4 kg. Her parents were healthy and had no family histories of similar diseases. Patient's physical examination showed body temperature 38°C, breathing rate 28 beats/minute, pulse rate 125 beats/minute, body weight 16 Kg, blood pressure 95/58 mmHg, normal consciousness, normal development, several palpable lymph nodes of about 1.0 cm × 1.0 cm on both sides of the neck, no tenderness, no adhesions, pharyngeal congestion, two superficial ulcers on the tongue, normal cardiopulmonary examination results, and no liver or spleen enlargement. On the first day of admission, she was given oseltamivir and G-CSF 5 μg/(kg.d)

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The authors declare that they have no competing interests.

Department of Pediatrics, First Hospital Affiliated to Bengbu Medical College, Bengbu Anhui, China.

** Correspondence: Jiali Xu, Department of Pediatrics, First Hospital Affiliated to Bengbu Medical College, Bengbu 233004, Anhui, China (e-mail: 2732910144@qq.com).*

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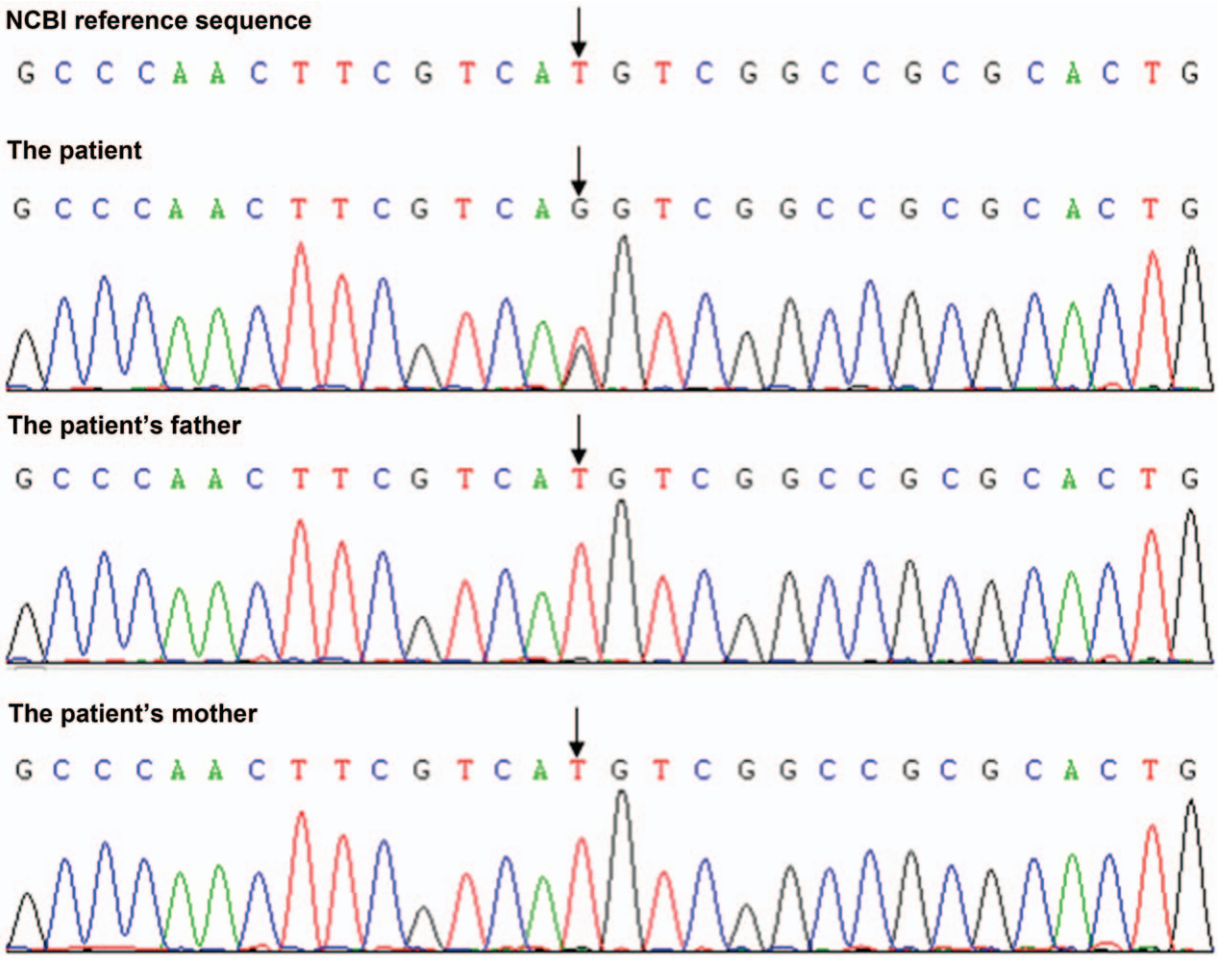

Figure 1. ELANE gene sequences of the patient and her parents.

treatment.[4] On the second day after admission, anti-TORCH antibody IgM, T.SPOT-TB test and anti-nuclear antibody spectrum were all negative, with normal globulin and T/B cell subsets. On the third day after admission, her throat swab test showed influenza A virus, and bone marrow exam was normal. On the fifth day after admission, blood routine test showed that ANC had increased to 1.6×10^9/L, so the G-CSF treatment was discontinued, and the patient was discharged. Given that the patient had a history of recurrent fever and oral ulcers as well as neutropenia, she was suspected to develop CyN. After discharge, the patient was closely followed-up and received regular blood routine monitoring (once every three days), and underwent testing for congenital neutropenia-related genes such as ELANE, HAX1, GF11, G6PC3, etc (high-throughput sequencing, Beijing Joy Orient Translational Medicine Research Center). The results showed a heterozygous mutation in ELANE gene (c.197T> G) (exon2) (p.M66R) (Fig. 1), which was not found in her parents. In addition, ANC was periodically reduced in the patient during follow-up, with an average duration of 21 days. Based on the periodic changes in ANC and ELANE gene mutation, the patient was diagnosed as CyN. The follow-up was continued till December 2017, during which the blood routine test was performed once per week. If neutropenia recurs, the patient would be given timely G-CSF treatment as well as active prevention and treatment of infection. The current growth and development of the patient is comparable with normal children of the same age, and incidence of fever and oral ulcers has significantly reduced (a total of three times during follow-up).

Genetic testing showed a heterozygous mutation in the ELANE gene (c.197T> G) (exon 2) (p.M66R), which was not found in her parents.

3. Discussion

CyN2 is a rare autosomal dominant disease caused by ELANE mutations.[5] Opportunistic infections can occur during ANC reduction, with the main clinical manifestations of fever, oral ulcers, gingivitis, pharyngitis, tonsillitis, skin infections, and swollen lymph nodes, whereas severe infections are very rare.[2,6,7] The patient in this report showed main clinical manifestations of fever and oral ulcers, without severe infection during ANC reduction. Boo et al.[2] reported a case of CyN caused by ELANE gene mutation, wherein the patient developed acute necrotizing fasciitis and severe sepsis, which was life-threatening and very rare.

Due to a lack of neutrophils, CyN children are prone to recurrent infections, and occasional serious infections that are life-threatening. Thus, regular monitoring of blood routine and timely prevention and control of infection, as well as G-CSF treatment are very important to control the disease in children.

The patient in this report and the case reported by Boo et al.,[2] were given anti-infection and G-CSF treatment, both of which achieved good results. With increasing age, some CyN2 children show gradual reduction in recurrent seizures, or even return to normal. Conversion to myelodysplastic syndrome or acute myeloid leukemia has not been reported in China and foreign countries. However, children suffering from severe congenital neutropenia (SCN) usually require long-term administration of G-CSF, and have risk of conversion to myelodysplastic syndrome or acute myeloid leukemia with the prolonged use of G-CSF and extension of life span.[8,9] Hematopoietic stem cell transplantation (HSCT) is an effective radical treatment, which can permanently correct any type of congenital neutropenia and is the only option for patients unresponsive to G-CSF treatment.

4. Conclusion

Herein, we reported a CyN proband due to ELANE gene mutation. This case highlights the importance of clinicians to be aware of the possibility of CyN in patients with repeated decrease in ANC, and timely detection of relevant genes is essential for a definitive diagnosis. Regular monitoring of ANC, active prevention and treatment of infection as well as G-CSF treatment is necessary for controlling CyN.

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