Severe congenital neutropenia mimicking chronic idiopathic neutropenia: a case report

Juhyung Kim¹, Soyoon Hwang², Narae Hwang³, Yeonji Lee⁵, Hee Jeong Cho¹, Joon Ho Moon⁶, Sang Kyun Sohn⁴, Dong Won Baek⁶

¹Department of Hematology/Oncology, Kyungpook National University Hospital, School of Medicine, Kyungpook National University, Daegu, Korea
²Department of Infectious Diseases, Kyungpook National University Chilgok Hospital, School of Medicine, Kyungpook National University, Daegu, Korea
³Department of Clinical Pathology, School of Medicine, Kyungpook National University, Daegu, Korea
⁴Department of Laboratory Medicine, Kyungpook National University Chilgok Hospital, Daegu, Korea
⁵Department of Internal Medicine, Kyungpook National University Hospital, Daegu, Korea
⁶Department of Hematology/Oncology, Kyungpook National University Chilgok Hospital, School of Medicine, Kyungpook National University, Daegu, Korea

Severe chronic neutropenia is classified as severe congenital, cyclic, autoimmune, or idiopathic. However, there is a lot of uncertainty regarding the diagnosis of severe congenital neutropenia (SCN) and chronic idiopathic neutropenia, and this uncertainty affects further evaluations and treatments. A 20-year-old man presented with fever and knee abrasions after a bicycle accident. On admission, his initial absolute neutrophil count (ANC) was 30/µL. He had no medical history of persistent severe neutropenia with periodic oscillation of ANC. Although his fever resolved after appropriate antibiotic therapy, ANC remained at 80/µL. Bone marrow (BM) aspiration and biopsy were performed, and a BM smear showed myeloid maturation arrest. Moreover, genetic mutation test results showed a heterozygous missense variant in exon 4 of the neutrophil elastase ELANE: c597+1G > C (pV190-F199del). The patient was diagnosed with SCN. After discharge, we routinely checked his ANC level and monitored any signs of infection with minimum use of granulocyte colony-stimulating factor (G-CSF), considering its potential risk of leukemic transformation. Considering that SCN can be fatal, timely diagnosis and appropriate management with G-CSF are essential. We report the case of a patient with SCN caused by ELANE mutation who had atypical clinical manifestations. For a more accurate diagnosis and treatment of severe chronic neutropenia, further studies are needed to elucidate the various clinical features of ELANE.

Keywords: Bone marrow examination; Granulocyte colony-stimulating factor; Leukemia; Mutation; Neutropenia

Introduction

Neutropenia is a hematological condition characterized by a reduced absolute neutrophil count (ANC) of < 1,500/µL [1]. Severe neutropenia with an ANC of < 500/µL increases susceptibility to serious bacterial or fungal infections [2]. Severe chronic neutropenia is classified as severe congenital, cyclic, autoimmune, or idiopathic. However, there is a lot of uncertainty regarding the diagnosis of severe congenital neutropenia (SCN) and chronic idiopathic neutropenia, and this uncertainty affects further evaluations and treatments. A 20-year-old man presented with fever and knee abrasions after a bicycle accident. On admission, his initial absolute neutrophil count (ANC) was 30/µL. He had no medical history of persistent severe neutropenia with periodic oscillation of ANC. Although his fever resolved after appropriate antibiotic therapy, ANC remained at 80/µL. Bone marrow (BM) aspiration and biopsy were performed, and a BM smear showed myeloid maturation arrest. Moreover, genetic mutation test results showed a heterozygous missense variant in exon 4 of the neutrophil elastase ELANE: c597+1G > C (pV190-F199del). The patient was diagnosed with SCN. After discharge, we routinely checked his ANC level and monitored any signs of infection with minimum use of granulocyte colony-stimulating factor (G-CSF), considering its potential risk of leukemic transformation. Considering that SCN can be fatal, timely diagnosis and appropriate management with G-CSF are essential. We report the case of a patient with SCN caused by ELANE mutation who had atypical clinical manifestations. For a more accurate diagnosis and treatment of severe chronic neutropenia, further studies are needed to elucidate the various clinical features of ELANE.

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The patient had a history of profound neutropenia with an ANC of < 200/µL, with bronchiolitis and asthmatic bronchitis occurring in the first 3 months of life. Whenever this patient arrived at the hospital during his childhood, his initial ANC was > 1,500/µL, which decreased to < 200/µL during his hospital stay (Fig. 1). Furthermore, his ANC returned to normal after appropriate antibiotic treatment. However, the patient had no regular periodic oscillations in his ANC (Fig. 1). He had a history of oral ulceration and glossitis when he was 13 years old; however, he had no history of parodontopathy, edentulism, or aphthosis. When he was 15 years old, the workup for neutropenia revealed a latent tuberculosis infection (LTBI). After 9 months of isoniazid treatment, the patient was cured of the LTBI. Since 2018, his ANC peak had decreased to < 1,300/µL. Nevertheless, he had never undergone BM examination or G-CSF treatment. Although the patient’s mother also had a history of neutropenia, a specific hematologic disorder was not identified in a BM study, and genetic testing, such as DNA sequencing, was not performed.

In May 2021, he was admitted to our hospital with fever and superficial soft tissue injuries caused by a bicycle accident. After admission to our infectious disease department, a physical examination revealed a body temperature of 38°C, blood pressure of 118/72 mmHg, pulse rate of 76 beats/min, and superficial abrasions over the proximal anterior tibia. At the time of admission, his complete blood count revealed a white blood cell count of 3,620/µL, ANC of 30/µL, hemoglobin level of 11.7 g/dL, platelet count of 209,000/µL, and serum C-reactive protein (CRP) level of 19.8 mg/dL. However, antinuclear antibody test results were negative. After he received piperacillin/tazobactam (4.5 g every 8 hours) for 3 days, his serum CRP level decreased to 6.2 mg/dL; his fever resolved on the second day of treatment. However, his ANC remained at 80/µL during the first 3 days (Fig. 2). The patient was referred to the hematology department, where BM aspiration and biopsy were performed. BM smear showed abnormal differentiation of the myeloid lineage (Fig. 3). The granulocytic series showed maturation arrest in the myelocyte stage with few segmented neutrophils (Fig. 3).

Based on the patient’s medical records, it was reasonable to begin G-CSF pending genetic testing. Lenograstim was administered to the patient at 2 µg/kg/day for 2 days. Although a G-CSF dose of 2–10 µg/kg/day is usually used for patients with SCN, we started with the lowest possible effective dose before confirming the presence of genetic mutations in this patient [8]. His ANC increased to 2,640/µL on the third day with 2 µg/kg/day lenograstim for 2 days. He was discharged from the hospital in a healthy condition after 7 days of treatment for severe neutropenia (Fig. 2). Finally, the genetic mutation test results showed that his severe neutropenia was caused by a heterozygous in-frame deletion in the neutrophil elastase ELANE, with a nucleotide substitution in intron 4 (IVS4+1G > C) located in the consensus splice donor site, resulting in a missense variant in exon 4 of ELANE: c597+1G > C (pV190-F199del) (Table 1, Supplementary Table 1) [9]. Therefore, the patient was diagnosed with SCN. Three weeks after discharge, his ANC decreased to < 500/µL.
Abruptly decreased ANC, 1 day after admission

No periodic change of ANC

Decreased baseline ANC

Fig. 1. Time courses of absolute neutrophil count (ANC) throughout the patient’s lifetime.

Nevertheless, the patient no longer had fever or signs of infection. G-CSF was not routinely administered and was reserved for episodes of infection.

Discussion

A nonfunctional, misfolded neutrophil elastase encoded by a mutated ELANE gene accelerates the apoptosis of granulocytic precursors of myeloid cells, causing myeloid maturation arrest [9,10]. ELANE gene mutations are the main cause of SCN and CyN [9]. Some researchers have considered SCN and CyN to represent a continuum with phenotypic variability [10]. It has been suggested that the clinical manifestations of patients with SCN and CyN might be influenced not only by a single genetic factor such as ELANE mutations but also by other genetic or epigenetic factors [11]. Therefore, it is possible to make an accurate initial diagnosis based on an accurate understanding of the pathogenic aspects of congenital neutropenia [12]. SCN is rare but can also be fatal. Furthermore, SCN has various phenotypes that are sometimes atypical, as in the present case.

Several reports have shown that the ANC is consistently < 200/μL in patients with SCN [6]. However, no evidence of constant severe neutropenia (ANC < 200/μL) was detected in our patient before 20 years of age. Severe neutropenia followed by recurrent infections is also a typical pattern of SCN and CyN [4]. In contrast, when the patient arrived at a hospital during his childhood, his initial ANC was > 1,500/μL, which decreased to < 200/μL during his hospital stay; this presentation was incompatible with SCN. Furthermore, the patient did not show regular periodic oscillations in his ANC. Therefore, it is possible to make an accurate initial diagnosis based on an accurate understanding of the pathogenic aspects of congenital neutropenia [12]. SCN is rare but can also be fatal. Furthermore, SCN has various phenotypes that are sometimes atypical, as in the present case. Therefore, it is possible to make an accurate initial diagnosis based on an accurate understanding of the pathogenic aspects of congenital neutropenia [12]. SCN is rare but can also be fatal. Furthermore, SCN has various phenotypes that are sometimes atypical, as in the present case.
Fig. 2. Time courses of absolute neutrophil count (ANC) during hospitalization. G-CSF, granulocyte colony-stimulating factor.

Fig. 3. Histopathology of the (A) peripheral blood and (B–D) bone marrow (Wright-Giemsa stain). (A) Neutrophils are present at high magnification (×1,000). (B) Hypercellularity is present at low magnification. Scale bar represents 100 μm. (C) Neutrophils are present at high magnification (×1,000). (D) The granulocytic series are hyperplastic and show a maturation arrest in the myelocyte stage with few segmented neutrophils. Scale bar represents 20 μm.
is considered a benign disease and is often self-limiting [2,7]. In young children, approximately 1/3 of CIN cases resolve spontaneously, whereas remission is uncommon in adults [5]. Thus, BM examination should always be considered when chronic neutropenia, which began in early childhood, persists. Considering that the risk of bacterial infection and leukemic transformation in ELANE-related neutropenia is high, precise diagnosis of SCN and early identification are essential for appropriate treatment with G-CSF and further management such as hematopoietic stem cell transplantation (HSCT) [16,17].

Extensive studies have shown that myeloid proliferation and maturation are stimulated by G-CSF, which can be used to treat severe chronic neutropenia [5,18]. However, since its introduction in 1998, G-CSF has attracted considerable attention owing to its potential risk of malignancy [5,19]. Recently, a strong relationship between G-CSF treatment and malignant transformation in SCN has also been reported [3,17]. In contrast, there is no evidence that G-CSF predisposes leukemic transformation in CIN and AIN [5]. Therefore, the dose, timing, and duration of G-CSF therapy should be very carefully determined in patients with congenital neutropenia, such as SCN and CyN [17,20]. Although we do not consider the long-term use of high-dose G-CSF unless there is sufficient evidence of infection, we do take G-CSF therapy and HSCT into consideration depending on how low the patient’s ANC level falls and the existence of any signs of infection [19].

Here, we report the case of a patient with SCN that mimicked CIN. We hope that patients with atypical features of SCN can be diagnosed in a timely manner and receive appropriate G-CSF treatment. Further studies are needed to elucidate the various clinical phenotypes of ELANE to obtain a more specific and precise diagnosis and treatment of severe chronic neutropenia. Moreover, clinical trials for patients with SCN to establish an appropriate ANC cutoff for G-CSF treatment are warranted to minimize the risk of malignant transformation, depending on the specific ELANE mutation.

### Notes

**Conflicts of interest**

No potential conflict of interest relevant to this article was reported.

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**Author contributions**

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**ORCID**

Juhyung Kim, https://orcid.org/0000-0002-5264-2406

Soyoon Hwang, https://orcid.org/0000-0003-3618-174X

Narae Hwang, https://orcid.org/0000-0001-7981-4661

Yeonji Lee, https://orcid.org/0000-0002-4186-4636

Hee Jeong Cho, https://orcid.org/0000-0001-8300-8179

Joon Ho Moon, https://orcid.org/0000-0003-3756-796X

Sang Kyun Sohn, https://orcid.org/0000-0002-1874-3959

Dong Won Baek, https://orcid.org/0000-0003-4446-1549

### References


### Supplementary materials

Supplementary Fig. 1 can be found via https://doi.org/10.12701/jyms.2022.00353.