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CASE REPORT
Reconstructive

Pyoderma Gangrenosum Secondary to Severe Congenital Neutropenia

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Summary: We encountered a case of a man who was diagnosed with severe congenital neutropenia as a child and presented at the age of 45 years with pyoderma gangrenosum (PG) of the lower leg. PG associates with an underlying systemic disease, most commonly inflammatory bowel, rheumatic, or hematological disease or malignancy. However, in many cases, the underlying disease was not known. Surgery can trigger PG. The histopathological features of PG were nonspecific, and diagnosis requires excluding other conditions that have a similar appearance. Our analyses showed that the PG in our case was secondary to severe congenital neutropenia, which had promoted an infection of keratinous cysts. The patient bore a mutation in the ELANE gene encoding neutrophil elastase. Only 1 other case of neutropenia-associated PG has been reported previously: the association was only suspected. The present complex case was effectively treated by systemic treatment of the neutropenia with granulocyte colony–stimulating factor and regional surgical treatment. Histology of the excised tissue revealed keratinous cysts that were diffusely distributed with inflammatory granulation tissue. We believe that the rupture of the walls of the keratinous cysts may have caused the PG. At the time of writing (3 years since the initial presentation), the PG has not recurred. This case shows the importance of performing detailed examinations, including blood tests, to determine the disease underlying PG. This was because if the underlying disease was identified, its treatment was likely to promote healing of the wound after local surgery and prevent recurrence. *(Plast Reconstr Surg Glob Open 2018;6:e1676; doi: 10.1097/GOX.0000000000001676; Published online 13 March 2018.)*

Pyoderma gangrenosum (PG) is a rare noninfectious neutrophilic dermatosis. Clinically, it starts with sterile pustules that progress rapidly and turn into painful ulcers of varying depths and sizes that have undermined violaceous borders. The legs are most often affected but other skin areas and mucous membranes can also be involved. The clinical course of PG ranges from mild to malignant, and it can present as a chronic or relapsing condition.[1,2] In 50% of cases, PG associates with an underlying systemic disease, particularly inflammatory bowel disease, rheumatic disease, hematological disease, and malignancy.[3] In 25%–50% of patients with PG, skin lacerations caused by trauma or surgery trigger new lesions.[4] PG is diagnosed on the basis of a history of an underlying disease, its typical clinical presentation, histopathology, and the exclusion of other diseases.[1] Plastic surgeons frequently encounter patients with chronic ulcers that require surgical treatment. We present here a rare case of PG associated with severe congenital neutropenia (SCN) that is effectively resolved by first treating the neutropenia.

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CASE REPORT

A 45-year-old man came to our department with fatigue and a swollen right lower leg that had a reddish exudate. The patient had been hospitalized several times as a child and was diagnosed with SCN. At that time, he was only given supportive treatment. In the ensuing decades, the patient had no symptoms. On presentation, he had

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40°C fever and a 20-cm–diameter circle of swelling on his right lower leg that was characterized by fistulae and pus discharge. Blood tests showed that the white blood cell and neutrophil counts were 295×10^2 and 2,500 cells/μl, respectively, whereas the C-reactive protein and glucose levels were 26 and 304 mg/dl, respectively (Fig. 1). During the week-long hospital stay, we washed the fistulae with saline every day and administered antibiotics, insulin, and ointment. The symptoms and laboratory values of the patient improved; his neutrophil counts rose to 9,100 cells/μl 7 days after presentation (Fig. 1). However, the neutrophils still only accounted for 8% of the total leukocytes: this was considerably lower than the healthy subjects (40%–70%). We expected that the fistulae of the erythema would eventually epithelialize.

However, the symptoms of the patient returned 1 week after discharge: the ulcers on his lower leg started expanding again, and his neutrophil counts dropped to 95 cells/μl. Moreover, some of the fistulae had connected with each other under the skin (Fig. 2). Given the clinical presentation and the patient's history of SCN, we suspected PG associated with SCN and the patient was rehospitalized. Furthermore, this patient had been affected with the diabetic mellitus because the chronic infection had impaired his glucose tolerance. Given his SCN, the patient was started on tridaily intravenous granulocyte colony–stimulating factor (G-CSF) treatment (5 μg/kg). He was also given subcutaneous insulin and intravenous antibiotic injections. During G-CSF treatment, his neutrophil counts rose rapidly: the count exceeded 500 cells/μl (20% of total leukocytes).

To prevent the leg ulcer infections from consuming neutrophils and to treat the expanding ulcers, we performed 2-step local surgery. In the first surgery, we excised the entire lesion at the sharp margin of the erythema and covered the wound with artificial dermis (Integra, New Jersey, USA) that was fixed using a negative pressure wound therapy device (PICO; Smith & Nephew, Tokyo, Japan). One week after the first operation, we removed the silicon membrane and applied an autologous skin mesh graft (14/1,000 inch) that had been excised from the left thigh. The graft was fixed using the same device. One week after the second operation, the skin graft exhibited perfect engraftment (Fig. 3). Histology showed the presence of keratinous cysts in the dermis that were diffusely distributed in fibrosing granulation tissue with granulomatous inflammation (Fig. 4). When the G-CSF treatment was discontinued after the second surgery, symptoms of other infectious diseases did not arise. At the time of writing (3 years since the initial presentation), there were no recurrences.

Bone marrow analyses showed that the severe congenital neutrophilia of the patient was caused by a mutation in the *ELANE* gene.

DISCUSSION

We experienced a rare case of lower leg PG underlaid by SCN. Although the diagnosis of PG is supported by biopsy histopathology, it is diagnosed primarily on the basis of clinical findings and the medical history, particularly the underlying diseases.[5]

Although the histopathological features of PG are nonspecific, they are valuable in terms of ruling out other

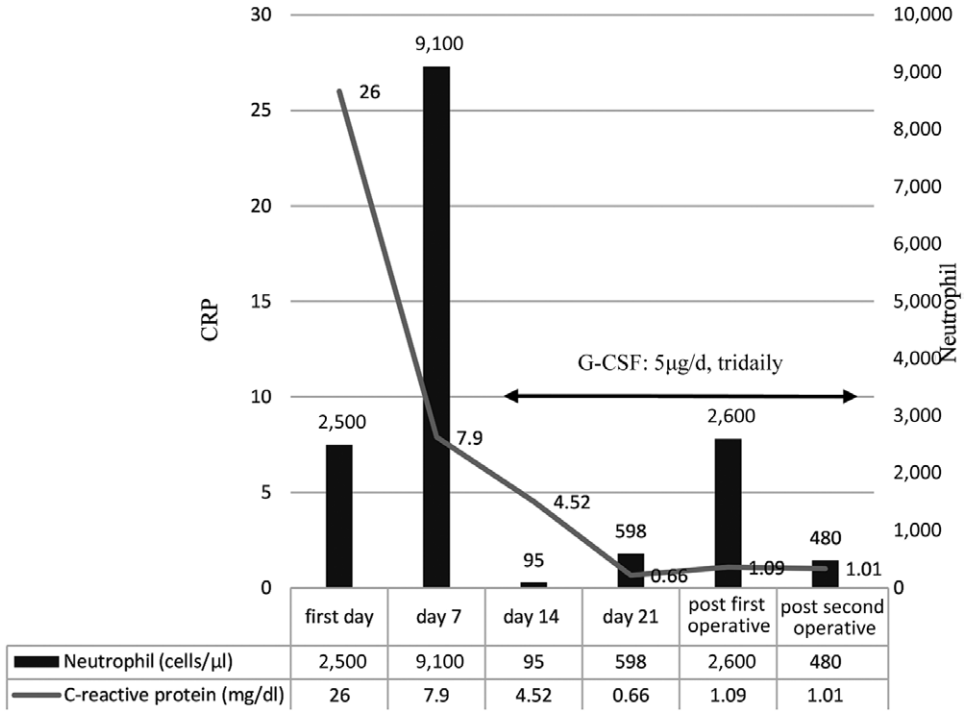

Fig. 1. The time course chart of blood examination from his first visit to the end of second operation. Bar graph shows the count of neutrophil. Gray line graph shows the value of C-reactive protein. CRP indicates C-reactive protein.

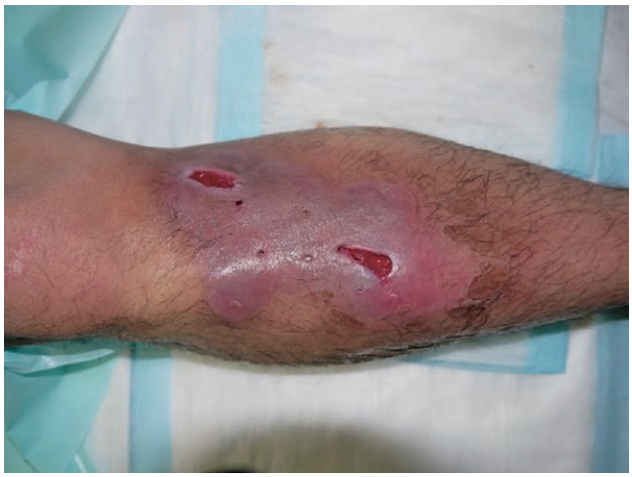

Fig. 2. Skin lesion of lower limb was a 20-cm–diameter circle of erythema associated with small ulcers. These ulcers had become bigger and connected with each other before surgery.

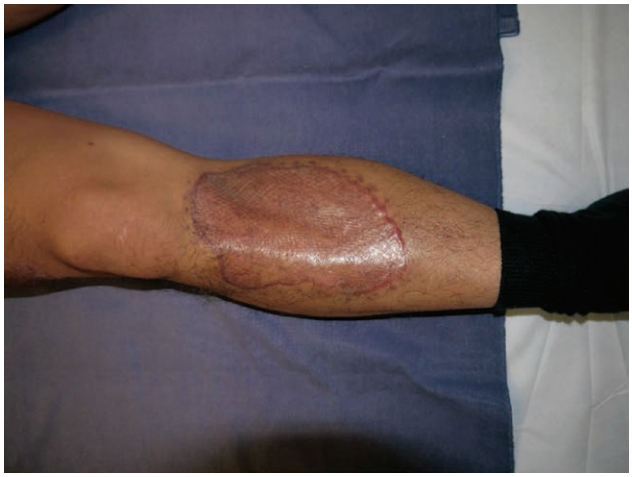

Fig. 3. The skin mesh graft was performed using NPWT as a reconstruction to the lesion of PG. Hundred percent engraftment of the skin mesh graft was observed. NPWT indicates negative pressure wound therapy.

causes of ulceration. Microscopic analysis of PG biopsy tissue reveals extensive neutrophilic infiltration, hemorrhage, and necrosis of the epidermis that resembles an abscess or cellulitis.[2] The treatment of PG involves wound care, topical medications, antibiotics for secondary infections, and treatment that aims to ameliorate or resolve the underlying disease.[2] The topical therapies include corticosteroids and the calcineurin inhibitor tacrolimus in the ointment form.[2,6] The most frequently used systemic medications include corticosteroids and/or cyclosporine.[7] Surgical procedures should only be performed as an adjunct to immunosuppression in patients with stable disease or partial remission.[1]

To the best of our knowledge, only 1 other adult case of PG associated with neutropenia has been reported.[8] In our case, our extensive analyses showed that the PG was the result of a inflammatory keratinous cyst that was secondary to SCN. The treatment of the neutropenia with G-CSF led to excellent outcomes and no recurrences. It would have been difficult to make this diagnosis had the patient not informed us of his SCN because, generally, progressive ulcers do not arise from keratinous cysts in noncompromised hosts.

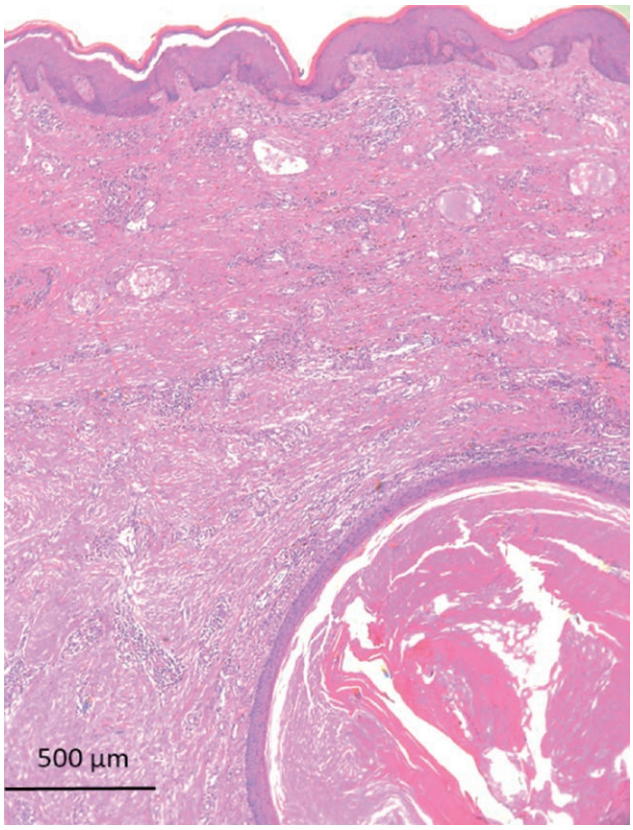

Fig. 4. There were keratinous cysts in the dermis that were diffusely distributed in fibrosing granulation tissue with granulomatous inflammation. Hematoxylin & eosin stain.

The fact that only 2 cases of PG associated with SCN have been reported to date suggests that this condition is rare. If PG is suspected, it will be necessary to determine the differential leukocyte counts, test for autoantibodies, and screen for malignancy. Measurements of the serum levels of coagulation factors, zinc, and glucose are also important for differentiating PG from the other causes of leg ulcer.

This is because proper treatment of the underlying disease will both promote the resolution of the PG and prevent its recurrence.

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