Clostridium septicum Myonecrosis in Congenital Neutropenia

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ABSTRACT. Severe congenital neutropenia (SCN) and Clostridium septicum myonecrosis is an uncommon and life-threatening association requiring urgent combined aggressive medical and surgical management. We report 2 cases of SCN (1 with known Kostmann’s syndrome and 1 not known at presentation to have a congenital neutropenic disorder but subsequently received a diagnosis of cyclic neutropenia) who presented with spontaneous C septicum myonecrosis. The cases highlight the importance of response to recombinant human granulocyte colony-stimulating factor in obtaining a satisfactory outcome for these patients. Early, empirical use of recombinant human granulocyte colony-stimulating factor in patients who are suspected of having a congenital neutropenia and who present with life-threatening sepsis is recommended. Pediatrics 2004;114:6757–6760. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-0124; congenital neutropenia, clostridium septicum, rh-GCSF.

ABBREVIATIONS. SCN, severe congenital neutropenia; rh-GCSF, recombinant human granulocyte colony stimulating factor.

Severe congenital neutropenia (SCN), incorporating congenital neutropenia (Kostmann’s syndrome), cyclic neutropenia, and idiopathic neutropenia, is a rare group of disorders characterized by a persistent neutrophil count of <0.5 x 10^9 per L. Patients with SCN often present with recurrent bacterial infections in the first few months of life commonly caused by Staphylococcus aureus, Escherichia coli, or Pseudomonas aeruginosa. The prognosis of patients with SCN has improved dramatically since the widespread availability of recombinant human granulocyte colony stimulating factor (rh-GCSF). Clostridial myonecrosis caused by Clostridium perfringens or C septicum is an uncommon, potentially fatal infection characterized by rapidly spreading fascial and muscle necrosis. Necrosis is produced by bacterial elaboration of α-toxin, a lecithinase capable of hydrolyzing essential components of mammalian cell membranes. Clostridium species are common in the human digestive tract, but C septicum is not a normal bowel flora. We report two cases of C septicum myonecrosis occurring in children with SCN and review the available literature on this topic.

CASE REPORTS

Case 1

The patient is a nondysmorphic boy who has nonconsanguineous parents and received a diagnosis of Kostmann’s syndrome at 2 months of age, when he presented with fever and neutropenia. The diagnosis was confirmed at 4 years of age, when genetic studies demonstrated an elastase-2 mutation, confirming the diagnosis on a molecular basis. After initial diagnosis at 2 months of age, the family was advised that in the event of a fever, the child would need urgent evaluation and would be placed on broad-spectrum antibiotics. This occurred on numerous occasions. Most of these admissions were of short duration, with fevers generally being attributed to viral illness. On 1 occasion, he developed a pulmonary abscess, but no specific organism was found. Trials of intravenous and subcutaneous rh-GCSF (Neupogen; Amgen, Thousand Oaks, CA) in low (5 μg/kg per day) and high doses (20 μg/kg per day) failed to illicit any improvement in the neutrophil count. Compliance with administration of rh-GCSF was suboptimal. A recommendation for sibling bone marrow transplantation was made but declined by the parents because of potential side effects. Given reports of Kostmann’s patients responding to rh-GCSF when concurrently placed on corticosteroids, a trial of low-dose daily oral dexamethasone was commenced but discontinued because of familial concerns of potential side effects.

At 5 years of age, 1 month after a single dose of dexamethasone, the patient presented with 12 hours of fever, 3 hours of vomiting, and 1 hour of pain over the left buttock and thigh. On arrival in the emergency department, he was found to be hypotensive and tachycardic. A 4-cm darkened area of skin over the lower right buttock was noticed on examination. The neutrophil count was 0.04 x 10^9 per L. He was started on inotropic support, broad-spectrum antibiotics, intravenous γ-globulin, rh-GCSF (10 μg/kg), and corticosteroids. Surgical management was undertaken within 5 hours of presenting to the emergency department. Necrotic areas of muscle and bone with skin crepitus suggesting gas gangrene were found to involve the entire right thigh and buttock and the lower paraspinal muscles. There was an additional isolated necrotic area of skin over the left shoulder. Laparotomy revealed extensive necrotic bowel. Considering the extent and rapid progression of necrosis, surgical salvage was deemed to be futile. The wounds were dressed and the patient was transferred to the intensive care unit, where he died 5 hours later. Bacterial culture from multiple biopsies isolated C septicum.

Case 2

The patient presented at 12 months of age with 4 days of pyrexia, mild lethargy, and anorexia. She was admitted to a local hospital, where a diagnosis of an upper respiratory tract infection complicated by obstructive airway disease was made. She was hospitalized and placed on oral antibiotics and inhaled steroids and β-2 agonists. She then developed an area of redness over the right thigh associated with increasing respiratory distress and tachycardia. She deteriorated rapidly, requiring ionotropic support and intubation for management of respiratory failure. She was then transferred to our tertiary-care institution.

On arrival to our institution, the area of redness had become discolored and progressed to involve the right side of the anterior and posterior abdominal wall. Laparotomy revealed a gangrenous caecum and extensive myonecrosis involving the full thickness of the anterior abdominal wall. Bowel resection and abdominal wall...
debridement were performed (Fig 1). Biopsies of these sites demonstrated *C. septicum* (Fig 2). A full blood count performed on admission demonstrated a total white cell count of $2.4 \times 10^9$ per L with a neutrophil count of $0.07 \times 10^9$ per L.

The patient’s history was reviewed and demonstrated multiple upper respiratory tract infections usually occurring every 3 to 4 weeks for which she had been treated with frequent courses of oral antibiotics. On a previous emergency department visit, at 4 months of age, a complete blood count was obtained. This demonstrated a neutrophil count of $0.0 \times 10^9$ per L. Repeat testing unfortunately was not performed, and the family was not made aware of this finding.

Approximately 20 hours after admission to our institution, the hematology service was consulted, and, in view of the possibility of the patient having SCN, she was placed on intravenous rh-GCSF ($10 \mu g/kg$ per day) $\sim 20$ hours after admission. The day after commencing rh-GCSF, the neutrophil count began to rise. A bone marrow aspirate was performed on that day; this demonstrated normal cellularity with left-shifted myelopoiesis and a paucity of mature neutrophils. During the first 3 days of presentation, she underwent additional resections of necrotic skin and subcutaneous tissue but stabilized the day after commencing rh-GCSF to the point of no longer requiring inotropic support. The patient continued on rh-GCSF, and the neutrophil count rose dramatically to $20.0 \times 10^9$ per L. She was then placed on every-other-day rh-GCSF ($10 \mu g/kg$) and on this dose and frequency of rh-GCSF has demonstrated a cyclic pattern with her neutrophil count falling for 3 to 4 days to $<0.5 \times 10^9$ per L every 17 days. This cyclic pattern (Fig 3) has continued despite treatment with rh-GCSF and is in keeping with the diagnosis of cyclic neutropenia. Fortunately, no additional septic events have occurred despite having undergone numerous surgical reconstructive procedures.

**DISCUSSION**

We report 2 cases of SCN presenting with *C. septicum* myonecrosis. The first case occurred in a child with SCN, who was known not to respond to rh-GCSF and who rapidly succumbed to the *C. septicum* myonecrosis despite early surgical intervention. This case reinforces the importance of response to rh-GCSF in improving the morbidity and mortality of children with SCN and provides additional support for investigating alternative, potentially curative therapies for children who have SCN and are refractory to rh-GCSF. The second case was not previously diagnosed to have a congenital neutropenic state, but a history of recurrent fevers, a low neutrophil count at 4 months of age, subsequent investigations, and the patient’s clinical course were consistent with a diagnosis of cyclic neutropenia. The patient responded to rh-GCSF, which was given before a definitive diagnosis was made. This case suggests a possible role for rh-GCSF as empirical treatment for young children who present with neutropenia and serious bacterial infections pending investigations to exclude the diagnosis of SCN.

Gut mucosal surfaces must maintain a delicate balance between protecting against pathogenic invasion and tolerating normal bacterial flora and dietary antigens. Neutrophils are critical to the normal defense against bacterial invasion of mucosal surfaces. After bacterial adhesion and local invasion, mucosal cells produce cytokines and effector molecules leading to upregulation of intraluminal T lymphocytes and recruitment of inflammatory cells, including neutrophils, to the site of infection. Transepithelial migration of neutrophils leads to intraluminal targeting of pathogens. Neutrophils possess important oxidative and nonoxidative microbialicidal systems. Nonoxidative antimicrobial systems are particularly crucial in anaerobic environments such as the gut.

*C. septicum* is a gas-producing, spore-forming bacilli found widely in the environment. *C. septicum* is not normal bowel flora, and unlike *C. perfringens*, *C. septicum* is relatively oxygen tolerant and can proliferate in the absence of significant tissue damage.
Spontaneous *C. septicum* infection is often associated with gastrointestinal and hematologic malignancies in adult patients. Anatomic abnormalities and malignant, necrotic areas associated with loss of bowel wall integrity facilitate germination of dormant spores, leading to proliferation, tissue invasion, and clinical infection. Alternatively, treatment with chemotherapy may lead to neutropenia, alteration of normal bowel symbionts, and mucosal ulceration, all of which predispose to invasion with clostridial species. Once invasion begins, clostridial infections spread rapidly, producing tissue necrosis through the elaboration of an α-toxin. Despite intensive medical and surgical therapy, *C. septicum* myonecrosis is associated with >80% mortality.

*C. septicum* infection has been previously reported in 8 children with neutropenia, described 2 cases of cyclic neutropenia and *C. septicum* infection treated with rh-GCSF. Both of these cases survived. A third case described in the same report did not receive rh-GCSF and died. Keogh et al. reported a patient who had SCN with *C. septicum* infection and responded to hyperbaric treatment, but no details of the severity of the neutropenia were reported. The remaining 4 cases occurred before the widespread availability of rh-GCSF, and all died. 

Rh-GCSF has dramatically improved the outcome of children with congenital neutropenia. Rh-GCSF acts on granulocytopenic progenitor cells to stimulate clonal proliferation of neutrophils, and it also improves neutrophil adhesion, chemotaxis, and phagocytic activity. An international registry established to monitor the progress of patients who have SCN and are treated with rh-GCSF recently reported data collected on 853 patients. The data show that 92.1% of patients respond to rh-GCSF at doses <30 μg/kg per day. Treatment with rh-GCSF in patients with cyclic neutropenia increases the amplitude of neutrophil oscillation and shortens the duration of severe neutropenia. The cause of the lack of response to rh-GCSF in a small percentage of patients with SCN is not understood. Bone marrow transplantation is the only effective therapy for patients with SCN refractory to rh-GCSF.

The combination of neutropenia and sepsis is seen in a variety of pediatric and neonatal scenarios. Overwhelming sepsis can lead to bone marrow suppression and depletion of bone marrow reserves, thereby presenting with neutropenia. Alternatively, sepsis in the presence of neutropenia may be the first indication of an underlying congenital neutropenia. When confronted with a neutropenic infant with sepsis, the issue of empirical treatment with rh-GCSF is often raised. Unfortunately, there are no studies specifically addressing the role of rh-GCSF in reversing sepsis-induced bone marrow suppression in children. There are a number of animal models in which the use of rh-GCSF has resulted in a reduction in sepsis-related mortality in a variety of neutropenic and nonneutropenic settings with various infections, including peritonitis, streptococcal infections, and infections associated with severe burns. In contrast, an increase in mortality and a decrease in bacterial clearance were shown in an animal model of Gram-negative bacterial pneumonia treated with rh-GCSF. In addition, a review of randomized studies of routine rh-GCSF administration in otherwise well (nonneutropenic) infants who presented with sepsis failed to demonstrate a significant clinical benefit. Despite this, judicious use of rh-GCSF in an infant who presents with sepsis and neutropenia may be justified while definitive investigations to exclude a congenital neutropenic state are being conducted. Our literature review as well as our experience in our second case shows that the use of rh-GCSF seems to be associated with an improved outcome in children who have congenital neutropenia and present with *C. septicum* myonecrosis.

**CONCLUSIONS**

*C. septicum* myonecrosis that occurs in patients with congenital neutropenia is an uncommon but life-threatening condition. Response to rh-GCSF with a rapid rise in neutrophil count seems to be associated with improved outcomes. Early treatment with rh-GCSF in young patients with severe sepsis and neutropenia may be justifiable while definitive investigations to exclude a congenital neutropenic state are being undertaken.

**ACKNOWLEDGMENTS**

C.B. is a recipient of the Baxter Bioscience Pediatric Hemostasis Fellowship at the Hospital for Sick Children. We acknowledge the assistance of Dr. Gino Somers, who provided the photographs of the histopathology section.

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*Pediatrics* 2004;114;e757
DOI: 10.1542/peds.2004-0124
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DOI: 10.1542/peds.2004-0124

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