

Clostridium septicum myonecrosis in a pediatric patient with a self-reported penicillin allergy

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Infections with *Clostridium septicum* are especially rare in pediatric patients. *C. septicum* is the most common cause of spontaneous myonecrosis and is usually associated with comorbid malignancy. Treatment of choice for cases of *C. septicum* myonecrosis is prompt and thorough surgical debridement and antimicrobial therapy with high dose penicillin. The experience and management of *C. septicum* infections in patients who are unable to take penicillin are not well described, and the optimal duration of therapy is largely unknown. We describe a case of spontaneous myonecrosis in a 14-year-old receiving cytotoxic chemotherapy for Burkitt's lymphoma who had an anecdotal history of a penicillin allergy. Her infection was initially treated with ceftazidime and metronidazole in concert with debridement but was ultimately cured with 3 weeks of intravenous penicillin therapy following a graded penicillin challenge in hospital. We observed a delayed inflammatory tissue response to a *C. septicum* skin, soft tissue infection that temporally corresponded to neutrophil reconstitution in our patient with severe neutropenia. Our experience demonstrates that *C. septicum* myonecrosis can present indolently and progress rapidly and highlights the need for clinical vigilance and repeat "second-look" surgeries. Our case also emphasizes the importance of de-labelling penicillin allergies.

KEYWORDS: *Clostridium septicum*, myonecrosis, penicillin allergy

Les infections à *Clostridium septicum* sont particulièrement rares chez les patients d'âge pédiatrique. Le *C. septicum*, qui est la principale cause de myonécrose spontanée, est généralement associé à des malignités. Le traitement de première intention de la myonécrose à *C. septicum* consiste à effectuer un débridement chirurgical rapide et minutieux et un traitement antimicrobien au moyen d'une forte dose de pénicilline. L'expérience et la prise en charge des infections à *C. septicum* ne sont pas bien décrites chez les patients qui ne sont pas en mesure de prendre de la pénicilline, et on ne connaît pas vraiment la durée optimale du traitement. Les auteurs décrivent le cas d'une myonécrose spontanée chez une adolescente de 14 ans qui a reçu une chimiothérapie cytotoxique pour traiter un lymphome de Burkitt et qui a une allergie non démontrée à la pénicilline. Son infection a d'abord été traitée par de la ceftazidime et du métronidazole, conjointement avec le débridement, mais a fini par être guérie au bout de trois semaines de traitement intraveineux à la pénicilline après un test de provocation graduel à la pénicilline à l'hôpital. Les auteurs ont observé une réponse inflammatoire tardive des tissus à une infection de la peau et des tissus mous au *C. septicum* qui correspondait temporellement à la reconstitution des neutrophiles chez la patiente atteinte d'une grave neutropénie. Selon leur expérience, la myonécrose à *C. septicum* peut se manifester sous forme indolente et progresser rapidement, ce qui fait ressortir l'importance de la vigilance clinique et des secondes interventions chirurgicales. Ce cas démontre également l'importance de désétiqueter les allergies à la pénicilline.

MOTS-CLÉS : allergie à la pénicilline, *Clostridium septicum*, myonécrose

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CASE PRESENTATION

A 14-year-old female with Burkitt's lymphoma presented to the emergency department of a pediatric hospital with a 1-day history of isolated severe suprapubic abdominal pain and vaginal bleeding. She was admitted for pain control and workup. She had just completed her first cycle of consolidation chemotherapy with rituximab, cytarabine, vincristine, and etoposide 7 days prior.

Her medical comorbidities included epilepsy, cerebral venous sinus thrombosis, hypothyroidism, and tonsillectomy. Her medications included levothyroxine and lamotrigine. She had reported allergies to bananas and penicillin (remote rash), which were verified by her parents. Her immunizations were up to date.

Her examination in the emergency department revealed that she was hemodynamically stable and afebrile. Her lower abdomen was diffusely tender without guarding or peritonitis. She had a right-sided peripherally inserted central catheter (PICC) line that was functioning well. The PICC site was unremarkable. Her initial investigations revealed pancytopenia with severe neutropenia (absolute neutrophil count 0.0). The WBC count was <0.1 cells/mm³ (normal range 5,000–10,000 cells/mm³), hemoglobin 61g/L (normal range 12.1–15.1 g/dL), and platelets 9 cells/mm³ (normal range 150,000–400,000 cells/mm³). The remainder of her laboratory tests, including her electrolytes, creatinine, liver enzymes, lipase, and amylase, were all within normal limits.

On her first day of admission, she became febrile at 38.3°C and was started empirically on ceftazidime 150 mg/kg/d for febrile neutropenia given her penicillin allergy. Blood and urine cultures were obtained and revealed growth of pan susceptible *Escherichia coli*. Her abdominal pain and vaginal bleeding subsided on her second day of admission, but she then developed sudden, severe right arm pain and swelling. She was thought to have developed an acute compartment syndrome and was promptly taken to the operating room (OR). Intra-operative tissue cultures grew light growth of *Clostridium septicum*.

Due to her penicillin allergy and overall clinical stability, metronidazole 30 mg/kg/d was added to her antibiotic regimen. She subsequently had three surgical debridements followed by placement of a vacuum-assisted closure (VAC) dressing. OR findings included progressive inflammation and increased tissue necrosis and fluid with dishwater appearance with each successive procedure. OR tissue samples were not sent to the pathology lab for assessment. An allergist was consulted, and she underwent a graded challenge with intravenous (IV) penicillin. She tolerated the full dose of IV penicillin without any adverse effects. Her antimicrobial therapy was changed from ceftazidime and metronidazole

to IV penicillin G 300,000 units/kg/d divided q 4 hours as monotherapy once her neutrophil count increased above 0.5×10^9 /L. She received a total of 3 weeks of targeted therapy with IV penicillin which was continued for 2 weeks after her final debridement. Her neutrophil count reconstituted 4 days after admission to hospital, and her creatinine kinase remained within the normal range throughout her hospitalization. Her lymphoma treatment was complicated by further episodes of febrile neutropenia, which were subsequently treated with piperacillin–tazobactam.

DISCUSSION

Originally described by Pasteur and Joubert in the late nineteenth century, *Clostridium septicum* is an anaerobic, spore-forming gram-positive bacillus that lives in the environment and is found in the intestinal microbiome of animals and humans (1–6). Along with other clostridial species, *C. septicum* can cause fulminant life- and limb-threatening infections (1). Whereas *Clostridium perfringens* is the most common cause of invasive clostridial infections, it is associated with penetrating trauma (5–7). *C. septicum* is the most common pathogen implicated in spontaneous myonecrosis (1–8).

Risk factors for developing *C. septicum* infections include malignancy (particularly gastrointestinal and hematologic malignancy), cyclical neutropenia, vascular compromise, and diabetes (1–9). In the absence of a diagnosed gastrointestinal malignancy or other established risk factor, many authors recommend screening for an occult colorectal malignancy with a colonoscopy given *C. septicum*'s association with malignancy (2). Due to a lower incidence of traditional risk factors amongst children, *C. septicum* infection is relatively uncommon. A comprehensive literature review and summary of pediatric cases of *C. septicum* infection has previously been reported by Smith-Slatas et al, who found that roughly half of all cases were associated with spontaneous myonecrosis (10). Myonecrosis and skin and soft tissue infections are the most frequent clinical syndromes associated with *C. septicum*, although bacteremia, osteomyelitis, aortitis, panophthalmitis, intra-abdominal infections, and central nervous system infections have also been described (3,11).

The natural history of *C. septicum* myonecrosis has a remarkable crescendo pattern. The disease has an indolent beginning, presenting with vague symptoms such as malaise and gastrointestinal complaints (1,2,6). Fever is frequent but not a necessity, while pain is nearly always present (1,10). Symptoms typically arise 6–48 hours after inoculation of tissue and, if left unchecked, fulminant necrosis and death follow within 24–48 hours of symptom onset (2,3,11,12).

The pathogenicity of *C. septicum* is imbued through the production of several toxins: α toxin, β toxin (DNase), γ toxin

(hyaluronidase), and δ toxin (heat-labile hemolysin) (2–4, 6,7). Alpha-toxin confers the ability to form fibrin pores and is the major virulence factor of *C. septicum* (1,6,11,13). Alpha-toxin is responsible for tissue necrosis, interstitial edema and hemolysis, vascular permeability, and hypotension characteristic of *C. septicum* infections (1,3,4,6,10,11,13). Swarming behaviour of pathogenic isolates of *C. septicum* in vitro has also been linked to α toxin and likely explains its ability to cause infection at distant sites of metastases following gut or genitourinary translocation (6,14).

C. septicum myonecrosis requires a multimodal treatment strategy. Prompt and thorough surgical debridements with routine “second-look” procedures in conjunction with antibiotics are necessary for successful treatment (1,2,4–7,10). Treatment with antimicrobial therapy alone is associated with poorer outcomes (6,7,10,12). The use of adjunct hyperbaric oxygen therapy to facilitate wound healing has been described; however, this practice currently lacks empiric data to support its use and is not routinely recommended, particularly if it delays surgical management (1,3,6,7,10). The use of hyperbaric oxygen for infections involving *C. septicum* may be of even less utility due to the relative aerotolerant nature of the organism (2,3,6,7).

Penicillin has anecdotally been the backbone of optimal antimicrobial therapy for *C. septicum* infections, but robust data is lacking (3,6,8–12). The concurrent use of clindamycin has been described early in the disease course to inhibit toxin production (3,5,6,8). Metronidazole, vancomycin, carbapenems, extended-spectrum cephalosporins, and chloramphenicol have been suggested as alternatives in patients who cannot receive penicillins (2,3,6,8,11,12). The optimal duration of therapy is largely unknown but should likely extend beyond the point the patient is systemically well and has undergone his or her final debridement procedure (2).

Despite source control interventions and active systemic antimicrobial therapy, mortality of infections caused by *C. septicum* remains in the vicinity of 50%–60% (1,3,5,8,10,11).

A unique element to our patient’s case was a lack of inflammatory response and frank myonecrosis observed during her first OR, which became more apparent during successive surgeries. This observation highlights the importance of routine second-look procedures. We postulate that the initial benign appearance of the surgical field was explained by the prompt surgical exploration (within 3 hours of symptom onset) due to the presumptive diagnosis of acute compartment syndrome. The successive necrosis seemed to correlate with the reconstitution of the patient’s neutrophil count, and we wonder whether this accounted for the delayed inflammatory response we observed. Neutrophil recruitment is important for invoking a second-wave inflammatory response and recruitment of monocytes and macrophages

(15). Furthermore, neutrophil reconstitution has been shown to increase the robustness of the inflammatory response via monocyte recruitment in neutrophil-deficient mice (15).

Our patient’s management was initially challenged by a self-reported allergy to penicillin, our antibiotic of choice. Sadly, this scenario is all too familiar, with penicillin being reported as the most common medication allergy among patients presenting to pediatric emergency departments (16). The incidence of reported penicillin allergy in the community is 10%–20%, whereas the true incidence of penicillin allergy (by skin testing) is in the realm of 1%–4% (17,18). Incidence of true penicillin allergy in oncology patients is similar to that of the general population (19). A penicillin allergy predicts an allergy to aminopenicillins, piperacillin, and first-generation cephalosporins that share similar R1-groups (cefadroxil and cephalexin) (17,18). Roughly 10% of patients with a penicillin allergy will cross-react with first-generation cephalosporins except for cephazolin, which does not share a similar R1 group; this risk decreases to <1% with third-generation cephalosporins (17).

Reactions perceived as antibiotic allergies acquired in childhood are usually carried forward into adulthood without review or reassessment and expose patients to a lifetime of alternative antibiotics that may be less effective, more expensive, and which result in more frequent side effects and increased antimicrobial resistance than desired regimens (20). Though there is an increased awareness of the pitfalls of penicillin allergies and a movement toward de-labelling patients using skin allergy testing and oral challenges, parents and providers remain resistant to removing allergies once they are catalogued (20).

This case reaffirms to us that health care practitioners routinely advocate for de-labelling (low-risk) penicillin allergies with drug challenges while patients are admitted to monitored units and engaged in health care to end the cycle of patients unnecessarily being denied penicillins—a class of highly effective, life-saving antibiotics and in many infections, the drug of choice.

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