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Case Report

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A Case of Necrotizing Fasciitis from *C. Septicum* in A Neutropenic Patient Undergoing Chemotherapy for Angioimmunoblastic T-Cell Lymphoma

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Introduction

Necrotizing fasciitis can present with skin involvement; however, it can become difficult to distinguish from the skin lesions of angioimmunoblastic T-cell lymphoma. *Clostridium septicum* is a common source of such infections.

Case Description

A 49-year-old man undergoing chemotherapy for angioimmunoblastic T-cell lymphoma presented with fevers, abdominal pain, and right shoulder pain. After an acute escalation in symptoms, necrotizing fasciitis with *Clostridium septicum* was diagnosed, primarily involving the right shoulder but with hematologic seeding. Urgent surgical debridement was performed, along with appropriately tailored antibiotic therapy. Despite aggressive treatment, the patient eventually succumbed.

Discussion

While an uncommon diagnosis, necrotizing fasciitis should be kept in mind as a source of fever in the appropriate clinical context of a neutropenic patient with skin findings, fevers, and pain. A delay in diagnosis and treatment could lead a fatal outcome.

Keywords: Angioimmunoblastic T-Cell Lymphoma; *C. Septicum*; Necrotizing Fasciitis; Neutropenia

Introduction

We present of a case of non-traumatic necrotizing fasciitis due to *Clostridium septicum* in a 49-year old male undergoing treatment for Angioimmunoblastic T-Cell Lymphoma (AITCL).

Necrotizing fasciitis is a life-threatening soft tissue infection

that can involve the epidermis, dermis, subcutaneous tissue, fascia, or muscle [1] Factors that can predispose to necrotizing fasciitis include penetrating traumas, surgical interventions such as obstetrics/ gynecological procedures, non-penetrating soft-tissue injuries such as a muscle contusion, and an immunocompromised state [1].

Necrotizing fasciitis is classified as Type I or Type II. Type I is polymicrobial, contains mixed aerobic and anaerobic organisms, and usually occurs in the elderly or in those with underlying disease such as diabetes or recent surgery. Type II arises from one bacterial species and can occur independently of any predisposing risk factors. Organisms that have been isolated from patients with necrotizing fasciitis include *Vibrio vulnificus* from those with liver cirrhosis who ingest raw oysters and *C. Septicum* in neutropenic patients with gas gangrene. Additional associated organisms include other *Clostridium* species, *Aeromonas hydrophila*, and *Streptococcus pyogenes* [1,2].

Infection with *Clostridium* species, including *C. perfringens*, *C. Septicum*, *C. novyi*, and *C. histolyticum* can be due to underlying medical conditions such as colon cancer, AIDS, hemodialysis, and inflammatory bowel disease [3] It has been theorized that the bacteria enter the blood via an ulceration or perforation in the gastrointestinal tract. Bacteria eventually migrate through the bloodstream to the site of infection [4].

Case Presentation

The patient is a 49-year old Hispanic male who originally presented with a two-year history of waxing and waning diffuse adenopathy that eventually became persistent. Accompanying clinical features included splenomegaly, numerous subcutaneous

nodules, and B symptoms. Biopsies of the skin and cervical lymph nodes were consistent with AITL. Staging evaluation demonstrated diffuse adenopathy involving the cervical, mediastinum, bilateral hilar, retroperitoneum and mesenteric regions, in addition to massive splenomegaly and extensive extranodal involvement including lungs and bone marrow consistent with stage IV disease, IPI XX, PiT score XX.

Despite the extensive burden, he presented with an excellent performance status and commenced therapy with dose-adjusted EPOCH (Etoposide, Prednisone, Vincristine, Cyclophosphamide, Doxorubicin) with fast clinical and excellent partial radiologic response but kinetic failure leading to abbreviation of the cycles as soon as counts recovered starting on cycle 2 and the addition of cyclosporine on cycle 3. Remissions were not durable, and precluded consolidation transplant. There was clear progression with fever and new skin lesions by cycle 5. Salvage therapy was attempted with BV-ICE (Brentuximab vedotin, Ifosfamide, Cisplatin, Etoposide) with no response. Romidepsin initiated as a single agent provided fast response, but approximately 1 month later the patient progressed with fever and skin lesions. Addition of pralatrexate led to control for another month, but again with similar progression. While waiting for insurance approval for lenalidomide, cyclophosphamide and prednisone were commenced with some palliation of symptoms. He was eventually started on lenalidomide 25 mg per day for 21 days in a 28-day cycle with dramatic response.

Approximately one month after starting lenalidomide, the patient presented to the emergency department with fatigue, fever, and left and right upper quadrant abdominal pain, which had been worsening over the previous three days. He also noted the development of a small, painful bruise at the right shoulder with no recollection of any trauma. He was hemodynamically stable at the time of interview, except for tachypnea. Examination revealed an ill-looking gentleman with massive hepatosplenomegaly. Notably, skin lesions idiosyncratic for the AITL were absent. He had a small, non-tender ecchymotic lesion at the right supraclavicular area without palpable crepitus. Laboratory work was significant for pancytopenia, most significantly an absolute neutrophil count of 140 cells/ μ L.

Chest x-ray showed fullness of the soft tissues at the right supraclavicular fossa. Computerized tomography (CT) of the abdomen and pelvis showed hepatosplenomegaly and intra-abdominal adenopathy, as well as diffuse wall thickening involving the distal/terminal ileum, cecum, and descending colon, questionable for typhlitis. Intravenous fluids and empiric cefepime were started after blood cultures were drawn. Within the next three hours, the ecchymotic lesion at the right shoulder rapidly progressed to involve the neck, deltoid, upper back, and chest accompanied by dramatically worsening pain, development of palpable crepitus, and septic shock (Figure 1).



Figure 1: Photograph depicting the large ecchymotic lesion at the right upper shoulder. No evidence of penetrating injury was obvious.

Repeat imaging showed extensive emphysema in subcutaneous and deep spaces of the right neck extending from level of lung apex to C1 vertebral body, strongly suggestive of necrotizing fasciitis (Figure 2).

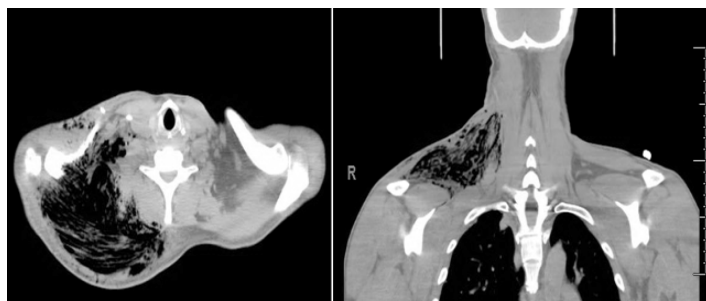


Figure 2: Transverse and coronal images demonstrating extensive subcutaneous emphysema at the right shoulder.

Antibiotics were escalated to vancomycin, clindamycin, and piperacillin/tazobactam. Emergent surgical debridement was performed. Wound and blood cultures grew *C. Septicum*. Histopathologic analysis of excised tissue showed mainly necrosis with bacterial colonies consistent with necrotizing fasciitis. Growth factor support was withheld given impressive splenomegaly and potential for splenic rupture.

Besides a large surgical wound managed with diligent wound care, aggressive medical support led to impressive recovery. The hallmark of his disease had been the skin lesions and none were present for nearly one month despite being off lenalidomide. Once the patient was stabilized in the hospital, therapy was restarted at the adjusted dose of 10 mg/day because of severe cytopenia and kidney dysfunction. Despite reinitiating lenalidomide, approximately 2 weeks later there was evidence of disease not only with skin lesions but also worsening respiratory status from progression of lung involvement by lymphoma. His condition slowly declined over the following weeks and he succumbed two months following admission.

Discussion

The patient in our case was infected with *C. Septicum*, a common cause of spontaneous, nontraumatic gas gangrene. This species is described as more aerotolerant than other clostridial organisms and more capable of non-traumatic tissue infection [4,5] A suspicious history of *C. Septicum* infection includes symptoms of unbearable pain, swelling, crepitus, and bulla formation.

C. Septicum is a gram-positive, anaerobic, spore-forming bacillus that can thrive in the anaerobic environment of host tissues, where it can produce virulent exotoxins [6,7]. The organism is found on human skin and gastrointestinal tract. Tissue trauma and subsequent hypoxia from poor blood supply allows for bacterial growth [8]. Nonspontaneous gas gangrene from *C. Septicum* is highly associated with malignancy as demonstrated by several case reports. Colon adenocarcinoma is the most common malignancy associated with *C. Septicum* infection; however, cases of lymphoma and leukemia have also been described [4] One such case highlights a 49-year-old woman with acute myeloid transformation of myelodysplastic syndrome who had undergone consolidation chemotherapy [8] Another case describes a 64-year-old woman with a history of chronic idiopathic neutropenia with multifocal metastasis of *C. Septicum* [9].

A literature review by Srivastava et al. in 2017 found 94 cases of spontaneous *C. Septicum* gas gangrene from 1956-2016. The prognosis in these cases is grim – overall mortality was 67%. Out of 40 cases with available information, 24 (60%) patients died within 24 hours of admission. Of the 76 adult (>18 years old) cases, 62 (78%) had a concurrent malignancy, 48 of which were gastrointestinal, and 7 of which were hematological. 100% of the patients with hematological malignancies died. Neutropenia was reported in 9/78 (11%) of cases [4].

Treatment for suspected necrotizing fasciitis involves immediate surgical exploration and debridement with broad-spectrum empiric antibiotics which may later be tailored to sensitivities if available [10]. For patients with neutropenia and suspected soft tissue infection, there is a strong recommendation with high-quality evidence by the Infectious Diseases Society of America (IDSA) for hospitalization and empiric antibacterial therapy with vancomycin plus antipseudomonal antibiotics such as cefepime, a carbapenem, or piperacillin-tazobactam. It is not routinely recommended by the IDSA for adjunct colony-stimulating factor therapy, granulocyte macrophage colony-stimulating factor, or granulocyte transfusion for neutropenic patients in suspected soft tissue infections [10].

The patient in this case had many of the published risk factors for infection with *C. Septicum*. The purported typhilitis seen on CT imaging may have predisposed to translocation of enteric *C. Septicum* across inflamed bowel mucosa, resulting in bacteremia.

Furthermore, he was immunosuppressed from the ongoing therapy with recent steroids, which augmented his susceptibility to a catastrophic infection. In addition, the skin lesions' fast response to lenalidomide increased areas of necrosis and hypoxia, predisposing to infection by *C. Septicum*.

Lymphoma has multiple systemic manifestations that can often obscure the clinical picture. The aggressive B symptoms and cutaneous manifestations in our case made the esoteric diagnosis of necrotizing fasciitis difficult to distinguish from another flare of his disease. While undoubtedly a quite uncommon diagnosis, given the appropriate clinical context it should be borne in mind as a potential source of neutropenic fever. It should also be emphasized that despite initial subtle presentation, this infection can rapidly deteriorate and survival hinges on immediate surgical intervention and optimization of the antibiotic regimen.

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