Case 64

The patient was a 30-year-old nursing student who was exposed 3 weeks prior to admission to his daughter who had chicken pox. Eight days prior to admission, he developed abdominal pain and fluid-filled lesions on his upper trunk and face which over the next week opened, crusted over, and began to heal. Because he continued to have fevers and abdominal pain, he was given oral acyclovir 4 days prior to admission. His family reported that a vesicle on his right buttock became enlarged and red at this time, and they treated it with hydrocortisone cream. One day before presentation he developed vomiting, shortness of breath, and pain and swelling of his left leg. He was admitted to his local hospital, and treatment with cefazolin and gentamicin was begun. He developed a respiratory rate of 50/min, his systolic blood pressure dropped to 60 mm Hg, and he became unresponsive. He was intubated and transferred to a university hospital.

At the new location, his antimicrobial coverage was changed to intravenous acyclovir and vancomycin. Admission laboratory results included increased bleeding times, creatinine of 4.0 mg/dl, creatine kinase (CPK) of 9,067 U/liter, aspartate aminotransferase (AST) of 173 U/liter, and alanine aminotransferase (ALT) of 58 U/liter. He was taken to the operating room, where he was found to have gross purulence in the calf tracking up to the thigh. The surgeons observed ischemic dead muscle interspersed with viable muscle tissue in the thigh area. Gram stain of a biopsy of the thigh is shown in Fig. 1. After surgery, the patient had a cardiopulmonary arrest and could not be resuscitated. Figure 2 shows the organism that was recovered from the patient's blood and tissue, growing on blood agar.

1. What is the likely organism infecting this patient with varicella? What pathologic process occurred in this patient?

2. What were the roles of chicken pox and hydrocortisone cream therapy in the development of his bacterial infection?

3. What was the likely source of his bacterial infection?

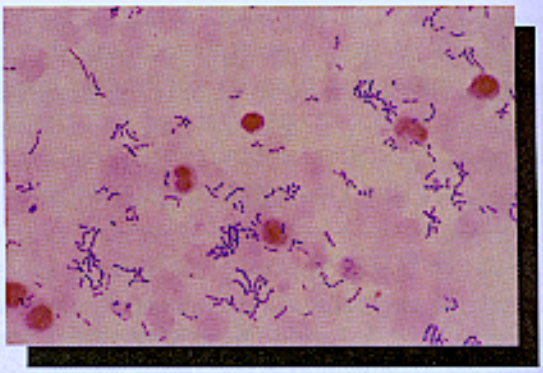

Figure 1

4. What virulence factor(s) does this organism produce that allows it to avoid phagocytosis?

5. What virulence factor(s) can this organism produce which acts as a superantigen? What is a superantigen? What features of this patient's clinical course are consistent with the pathologic effects of superantigens? What other organism(s) produces superantigens?

6. What other syndrome caused by this organism is associated with superantigen production?

7. Why has it been difficult to develop a vaccine against this organism?

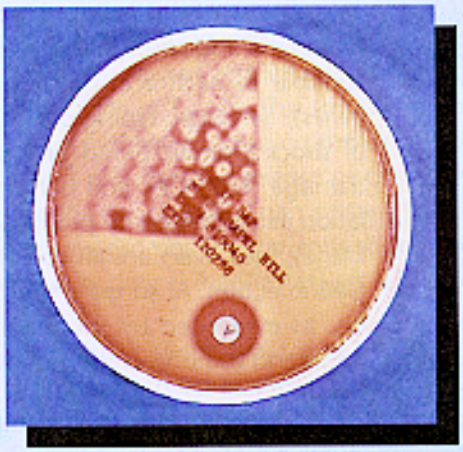

Figure 2

64

Case Discussion

1. On Gram stain, the organism was a gram-positive coccus in chains, which is consistent with *Streptococcus* species. The organism growing on blood agar is beta-hemolytic and susceptible to an "A" disk, or bacitracin. Streptococci which are susceptible to bacitracin generally are group A streptococci (GAS; *Streptococcus pyogenes*). Serologic typing of the isolate confirmed that it was GAS. The development of shock (systolic blood pressure of 60 mm Hg), bacteremia, extensive soft tissue damage (high CPK and ischemic, dead muscle), disseminated intravascular coagulation as evidenced by prolonged bleeding times, and multiple organ failure (lungs, kidney, and liver) are all consistent with toxic shock-like syndrome associated with GAS infection. At surgery, this patient was also found have to have necrotizing fasciitis, as evidenced by the finding of gross purulence tracking from the calf to the thigh and the observation of necrotic muscle interspersed with viable muscle tissue.

2. Chicken pox (varicella-zoster virus infection) is believed to predispose patients to invasive GAS disease in two ways. First, the pox lesions cause breaks in the skin and can act as a portal of entry for the bacteria. Second, and more controversially, some investigators believe that varicella-zoster virus is immunosuppressive and that infections with this virus render individuals more susceptible to secondary bacterial infection. Hydrocortisone cream would be locally immunosuppressive, helping the GAS evade the host's immune system during the initial stages of infection. In a recent study, 13% of individuals with invasive GAS infections had prior or concurrent varicella infections.

3. GAS can colonize the skin and can be asymptomatically carried in the throat. Given the location of the patient's original infection, the right buttock, it is likely that his skin was colonized with the organism. The breakdown in skin integrity caused by the varicella infection provided a portal of entry for GAS.

4. GAS strains produce an antiphagocytic cell wall component called M protein. The antiphagocytic activity of M protein is due to the organism's ability to inhibit the activation of the alternate complement pathway. Activation of this pathway is important in the opsonization of bacteria such as GAS. Antibodies to M protein can neutralize the antiphagocytic effect of this cell wall component. Unfortunately there are over 80 different M types, and immunity to one type does not necessarily confer immunity to another.

GAS organisms may also produce a hyaluronic acid capsule. However, this capsule is not produced by all GAS isolates and probably plays a secondary role in the organism's ability to evade phagocytes.

5. M protein and the pyrogenic exotoxins A, B, and C, all produced by GAS, have been reported to act as superantigens. The specific M types M1 and M3, which produce the pyrogenic exotoxin A, have been associated with the recent resurgence in invasive GAS disease. This patient's isolate was an M1 type that produced pyrogenic exotoxin A.

To understand what a superantigen is, it is important to understand the difference between the interaction of an antigen and that of a superantigen with the immune system. It is estimated that an antigen stimulates approximately 1 in 10,000 T cells after it is processed ("presented") by an antigen-presenting cell (macrophage or macrophage equivalent). By contrast, superantigens do not require processing by macrophages and nonspecifically stimulate up to 20% of T cells. This stimulation of large numbers of T cells leads to massive release of cytokines including tumor necrosis factor (TNF), interleukin-1, and interferon. It is this massive release of cytokines which is believed to be responsible, in part, for the shock and organ system failure that are seen in patients with the toxic shock-like syndrome. The patient's shock and kidney, liver, and lung failure are all consistent with clinical manifestations resulting from the activity of superantigens.

The enterotoxins A through G and the toxic shock syndrome toxin-1 (TSST-1) produced by *Staphylococcus aureus* all have been noted to act as superantigens. The toxic shock syndrome caused by TSST-1-producing strains of *S. aureus* is the prototypic superantigen-induced disease.

6. Streptococcal pyrogenic exotoxins A through C were once referred to as erythrogenic or scarlet fever toxins. Scarlet fever is a complication of pharyngitis caused by a pyrogenic exotoxin-producing strain of GAS. The skin rash seen in scarlet fever is believed to be superantigen mediated.

7. The molecule that has been the most attractive target for the development of a GAS vaccine is the M protein. This protein is known to play an important role in evasion of the immune system; it is located on the cell surface, and with modern biochemical techniques, it is fairly easy to purify. However, epitopes of M protein have been shown to share antigenic properties with several human tissue components including myosin and sarcolemmal membrane proteins. Therefore, vaccines against M proteins have the potential to induce antibodies which could bind and damage a variety of tissues. In fact, it is the production of antibodies to the M protein which is believed to be an important factor in the pathogenesis of two potential post-GAS nonsuppurative sequelae, rheumatic fever and glomerulonephritis.

The challenge of making a vaccine against the M protein component of GAS is to identify M protein epitopes that will induce the production of protective antibodies against as many different M types as possible while at the same time ensuring that the antibodies raised against these epitopes will not react with human tissues.

References

1. **Kiska, D. L., B. Thiede, J. Caracciolo, M. Jordan, D. Johnson, E. L. Kaplan, R. P. Gruninger, J. Lohr, P. H. Gilligan, and F. W. Denny.** Invasive group A streptococcal infections in North Carolina: epidemiology, clinical features, and genetic and serologic analysis of causative agents. Submitted for publication.

2. **Kolb, M.** 1995. Bacterial pyrogenic exotoxins as superantigens. *Clin. Microbiol. Rev.* **8**:411–426.