CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 2-2009: A 25-Year-Old Man with Pain and Swelling of the Right Hand and Hypotension

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PRESENTATION OF CASE

Dr. William D. Binder (Emergency Services): A 25-year-old man was transferred to the emergency department of this hospital because of pain and swelling of the right hand and hypotension.

The patient had been well until 2 days earlier, when he noticed a lesion on the dorsum of his right hand, which he thought was an insect bite. The next day, the hand became swollen and painful, and he felt ill. In the evening, he had difficulty using his hand while working on a computer. The next morning, he had chills, and his temperature rose to 38.6°C. At 5 p.m., the patient's mother returned home and found him obtunded, vomiting, and incontinent of feces and urine. His temperature was 38.6°C. He was taken by emergency medical services to the emergency department of another hospital.

The patient appeared acutely ill and confused. The blood pressure was 73/25 mm Hg, the temperature 37.9°C, the pulse 145 beats per minute, the respiratory rate 30 breaths per minute, and the oxygen saturation 100% while the patient was breathing 6 liters of oxygen by nasal cannula. The skin appeared cyanotic and was cool. The right hand was mottled and swollen, with a black eschar, 1 cm in diameter, on the dorsum; the swelling extended up the proximal forearm. Capillary refill occurred in 4 seconds. The patient was able to move his fingers, but the range of motion was limited. Laboratory-test results are shown in Table 1. The right arm was immobilized on pillows. Specimens of blood were sent for culture. Electrocardiography showed sinus tachycardia and nonspecific ST-segment and T-wave changes. Two peripheral intravenous lines, a triple-lumen internal jugular line, and a urethral catheter were inserted. There was little urinary output, and the stool was heme-positive.

During 3.6 hours in the emergency department, 10 liters of crystalloid solution were infused intravenously, as were ceftriaxone, methylprednisolone, diphenhydramine, piperacillin and tazobactam sodium, pantoprazole, naloxone, potassium chloride, and magnesium sulfate. One dose each of acetaminophen and tetanus toxoid was given, and norepinephrine was administered, with the dose adjusted to maintain a mean arterial pressure of more than 65 mm Hg. The skin became less cyanotic, and a

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flushed, deep-red color developed; blue discoloration persisted over the fingers of the right hand distally. Urinary output improved. Computed tomography (CT) of the right hand, performed without contrast material, showed soft-tissue swelling along the dorsum of the hand, with extension to the level of the extensor tendons. There was no subcutaneous air, loculated fluid collection, intramuscular abscess, or destruction of bone. The patient was transferred to the emergency department of this hospital, arriving 1.4 hours later. Medications administered during transfer included norepinephrine (for blood pressure) and morphine (as needed, for pain).

Table 1. Hematologic and Blood Chemical Laboratory Data.*

Variable	Reference Range, Adults (This Hospital)†	Other Hospital, on Admission	This Hospital, on Admission
Hematocrit (%)	41.0–53.0 (men)	57.3	44.0
Hemoglobin (g/dl)	13.5–17.5 (men)	19.9	15.9
White-cell count (per mm^3)	4,500–11,000	13,000	17,900
Differential count (%)			
Neutrophils	40–70	36	32
Band forms	0–10	22	24
Lymphocytes	22–44	6	0
Monocytes	4–11	8	3
Eosinophils	0–8	2	0
Metamyelocytes	0	20	40
Myelocytes	0	6	1
Platelet count (per mm^3)	150,000–350,000	187,000	133,000
Activated partial-thromboplastin time (sec)	22.1–34.0		41.9
Prothrombin time (sec)	10.3–13.2		18.5
Prothrombin time (international normalized ratio)			1.8
Glucose (mg/dl)	70–110	74	118
Sodium (mmol/liter)	135–145	140	141
Potassium (mmol/liter)	3.4–4.8	2.8	3.6
Chloride (mmol/liter)	100–108	101	110
Carbon dioxide (mmol/liter)	23.0–31.9	24	21.0
Urea nitrogen (mg/dl)	8–25	22	22
Creatinine (mg/dl)	0.6–1.5	3.9	2.4
Bilirubin (mg/dl)			
Total	0.0–1.0	0.9	0.9
Direct	0–0.4		0.4
Total protein (g/dl)	6.0–8.3	6.3	4.1
Albumin	3.3–5.0	3.6	2.5
Globulin	2.6–4.1		1.6
Phosphorus (mg/dl)	2.6–4.5	3.2	2.8
Magnesium (mmol/liter)	0.7–1.0	0.6	0.6
Calcium (mg/dl)	8.5–10.5	9.0	7.0
Ionized calcium (mmol/liter)	1.14–1.30		1.09

Table 1. (Continued.)

Variable	Reference Range, Adults (This Hospital)†	Other Hospital, on Admission	This Hospital, on Admission
Creatine kinase (U/liter)	60–400 (men)	1,886	2,934
Isoenzymes (ng/ml)	0.0–6.9	36.6	71.3
Isoenzyme index (%)	0.0–3.5	1.9	2.4
Troponin I	Negative	Negative	Negative
Troponin T (ng/ml)	0.00–0.09		<0.01
Lactic acid (mmol/liter)	0.5–2.2	7.5	2.3
Alkaline phosphatase (U/liter)	45–115	78	35
Aspartate aminotransferase (U/liter)	10–40	64	123
Alanine aminotransferase (U/liter)	10–55	47	72
Lipase (U/dl)	1.3–6.0		0.9
Amylase (U/liter)	3–100		32
Alcohol (mg/dl)	<10	<10	
Toxicology screen		Presumptively positive for methadone, otherwise negative‡	
Blood gas (with 100% inspired oxygen; temperature, 37.2°C)			
Source		Arterial	Not specified
pH	7.32–7.45	7.30	7.26
Partial pressure of carbon dioxide (mm Hg)§	35–50	37.1	45
Partial pressure of oxygen (mm Hg)§	40–90	198	56

* To convert the values for glucose to millimoles per liter, multiply by 0.05551. To convert the values for urea nitrogen to millimoles per liter, multiply by 0.357. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for bilirubin to micromoles per liter, multiply by 17.1. To convert the values for phosphorus to millimoles per liter, multiply by 0.3229. To convert the values for magnesium to milliequivalents per liter, multiply by 2. To convert the values for calcium to millimoles per liter, multiply by 0.250.

† Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are for adults who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.

‡ The sample was drawn after the administration of naloxone.

§ The reference range for the partial pressure of carbon dioxide at the other hospital was 35 to 45 mm Hg, and the reference range for the partial pressure of oxygen 80 to 100 mm Hg.

The patient had seasonal allergies. As a child, he had undergone myringotomies and an inguinal herniorrhaphy, and his wisdom teeth had been extracted. He was allergic to sulfamethoxazole, which had caused desquamation. He lived with his family on a farm in New England, had worked in the construction industry, and was exposed to horses, dogs, and cats. He hunted, most recently 7 months earlier, and had not traveled recently. His mother reported that the patient had recently had abscesses on his left chin and buttocks, which he had treated with warm compresses. He had also recently taken a course of prednisone for a persistent cough and took cetirizine, as needed, for allergies. He smoked cigarettes and drank alcohol socially; he did not use intravenous drugs. His parents were well; other family members had diabetes, hypertension, and thyroid disease.

On examination in the emergency department, the patient appeared ill and lethargic but was easily aroused and became oriented. The temperature was 37.3°C and rose to 37.9°C within 20 minutes. The blood pressure was 92/50 mm Hg, the pulse 129 beats per minute, the respiratory rate 28 breaths per minute, and the oxygen saturation was 96% while he was breathing 100% oxygen

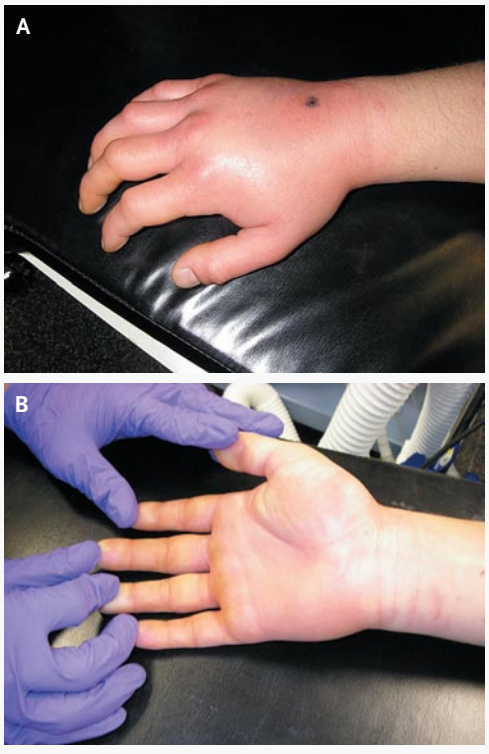

Figure 1. Clinical Photographs of the Hand at Presentation.

The small, innocuous-appearing wound on the dorsum of the hand (Panel A), with swelling and erythema, is consistent with cellulitis. Also shown is the volar aspect of the hand (Panel B).

through a nonrebreathing mask. Jugular venous distention was 10 cm, measured at a 45-degree angle. Crackles were present in both lungs. There was a brown circular area of necrotic skin, 2 cm in diameter, on the mid-dorsum of the right hand, with two central pinpoint marks (Fig. 1A). The soft tissue of the hand and wrist was erythematous and swollen over the palmar and dorsal surfaces to the proximal forearm (Fig. 1B), and it was exquisitely tender when palpated. The fingers of the right hand were held in flexion; sensation of light touch was intact in the distribution of the radial, ulnar, and median nerves, and radial and ulnar pulses were 2+ on palpation. The patient was unable to move the fingers of the right hand more than 2 to 3 mm, and passive motion of the fingers induced severe pain. There was no crepitation. Petechiae were present on both legs. The remainder of the examination was normal. Results of laboratory tests are shown in Table 1. A radiograph of the hand revealed prominent soft-tissue swelling, predominantly along the dorsum of the hand; no radiopaque foreign body or subcutaneous air was identified. A chest radiograph showed perihilar opacities and blurring of the pulmonary vasculature, findings that were consistent with interstitial edema. An internal jugular venous catheter terminated in the superior vena cava.

Vancomycin and clindamycin were administered intravenously, and norepinephrine was continued. A procedure was performed.

DIFFERENTIAL DIAGNOSIS

Dr. Michael R. Filbin: I am aware of the diagnosis in this case. This previously healthy young man presented to the emergency department with shock, presumably due to a rapidly progressive infection involving his right hand and forearm. May we see the radiographic images?

Dr. Laura L. Avery: An axial CT image of the right hand obtained at the other hospital shows diffuse soft-tissue swelling superficial to the extensor tendons throughout the dorsum of the hand (Fig. 2A). There is no evidence of loculated fluid collection or abscess formation in the deep musculature. Plain films of the hand show soft-tissue swelling along the dorsal and palmar surfaces without evidence of bone destruction (Fig. 2B and 2C). The chest radiograph obtained on admission to this hospital showed perihilar opacities blurring the pulmonary vasculature, a finding that was consistent with pulmonary edema.

Dr. Filbin: This patient has severe sepsis, a diagnosis based on a temperature greater than 38.0°C, a heart rate of more than 90 beats per minute, respirations of more than 20 breaths per minute, a white-cell count of more than 12,000 per cubic millimeter, and evidence of organ dysfunction; the organ dysfunction places him at increased risk for death.[1] The patient also has septic shock, as defined by the presence of persistent hypotension (systolic blood pressure <90 mm Hg) despite adequate volume resuscitation. In this case, the working diagnosis was septic shock due to necrotizing fasciitis involving the right hand and forearm.

DISCUSSION OF MANAGEMENT

EARLY GOAL-DIRECTED THERAPY FOR SEPTIC SHOCK

Septic shock is associated with a mortality rate of 30 to 50%. This patient's condition therefore re-

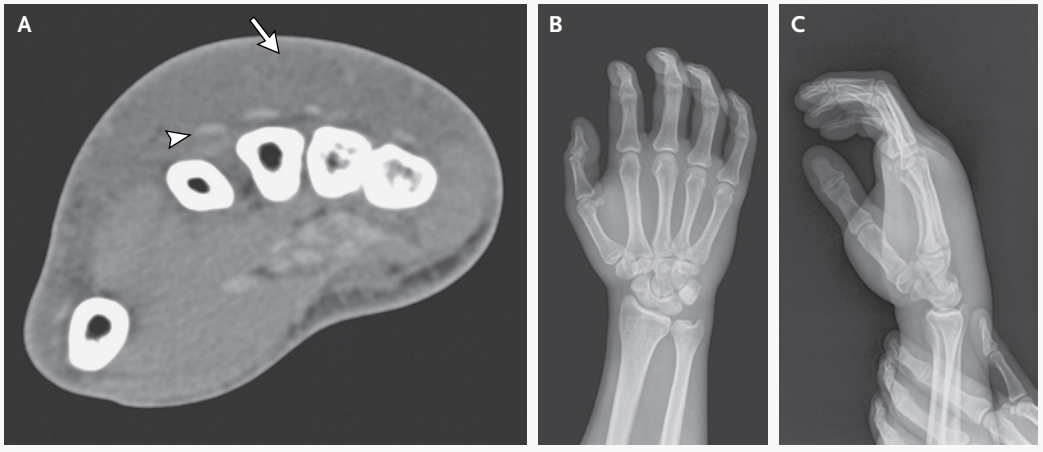

Figure 2. Radiographic Images of the Hand.

An axial image from a CT scan of the right hand obtained at the other hospital, without intravenous contrast material, shows soft-tissue swelling overlying the dorsum of the hand (Panel A, arrow). The soft-tissue abnormality extends deeply into the hand, to the level of the extensor tendons (Panel A, arrowhead). No subcutaneous air or loculated fluid collections were identified, and no osseous destruction was identified. Anteroposterior and lateral views of the right hand (Panels B and C, respectively) show prominent soft-tissue swelling along the dorsum of the hand.

quired urgent, aggressive management on his admission to the emergency department of the other hospital. The keys to treating his septic shock were restoring tissue perfusion, providing prompt administration of antimicrobial therapy, and removing the source of infection. Early goal-directed therapy, a three-part algorithm for managing septic shock, is associated with a significant decrease in the risk of death when initiated soon after a patient's admission to an emergency department.[2]

The first objective in early goal-directed therapy is to provide adequate volume resuscitation, which is usually achieved through rapid intravenous administration of crystalloid fluid (a 500- to 1000-ml bolus of normal saline every 30 minutes). This patient received aggressive fluid resuscitation through a central venous catheter until there was evidence of volume overload. His central venous pressure remained at 7 mm Hg, just below the normal value (8 to 12 mm Hg), indicating the presence of ongoing peripheral vasodilatation.

If initial fluid resuscitation fails to restore adequate tissue perfusion, as it did in this case, the second step in early goal-directed therapy is to use vasopressors to maintain mean systemic arterial pressure above 65 mm Hg. Norepinephrine was used in this case; it is the vasopressor of choice because it results in peripheral vasoconstriction without causing clinically significant tachycardia. By the time the patient arrived at this hospital, he had hypotension, despite having received aggressive crystalloid resuscitation and vasopressor support. There was also evidence of pulmonary capillary dysfunction, including tachypnea, rales on auscultation of the chest, and detection of pulmonary infiltrates on chest radiographs — all signs of the development of the acute respiratory distress syndrome and volume overload. In such a case, endotracheal intubation should be strongly considered to prevent sudden respiratory collapse. However, this patient's condition remained stable, and we were able to avoid intubation.

The third objective is to achieve adequate tissue perfusion, as measured by central venous oxygen saturation. This patient was awake and alert, with an adequate respiratory effort, and did not require mechanical ventilation. Other strategies used to achieve adequate tissue perfusion, which did not prove necessary in this case, include increasing the concentration of oxygen-carrying hemoglobin or increasing cardiac output with an inotropic agent, such as dobutamine.

In addition to early goal-directed therapy, timely and appropriate antibiotic administration has been shown to reduce the mortality rate significantly.[3] Initial coverage should be broad, with treatment for gram-positive, gram-negative, and anaerobic species. Vancomycin was used in this

patient because of the possibility of community-acquired methicillin-resistant *Staphylococcus aureus.* Clindamycin was used for its superior action against group A streptococcus, an organism often found in necrotizing fasciitis.

The maintenance of tissue perfusion, blood pressure, and oxygenation and the administration of antimicrobial therapy are temporizing measures that are used until surgical exploration and removal of the source of infection are performed. The patient was taken to the operating room 4.25 hours after arrival in our emergency department.

SURGICAL MANAGEMENT OF NECROTIZING FASCIITIS

Dr. David C. Ring: In evaluating this patient's infected arm in preparation for surgery, I first looked for an appropriate operative target, such as an abscess, a closed-space infection, septic arthritis, or osteomyelitis. The absence of such a target usually suggests a simple cellulitis, which is generally not an indication for surgery. Clues to a more serious infection would be crepitation with palpation of the skin or visible gas, either in the skin or on imaging studies — both were absent in this patient. The clue that pointed to a more severe infection than simple cellulitis was the combination of extreme pain on finger motion or palpation and severe septic shock. In view of these findings, I considered the infection to be life-threatening and immediately had the patient taken to the operating room for biopsy and definitive treatment.

On incision, clues such as fat necrosis (often referred to as dishwater pus) and thrombosis of subcutaneous veins (sometimes called spider-web veins) would suggest necrotizing fasciitis. The former (Fig. 3A), but not the latter, was present in this patient. The surgeon must remove involved fascia and overlying skin and, in severe cases, underlying muscle, until all infected and devitalized tissue has been removed. It is essential to work closely with a pathologist, who provides critical feedback, determining when all histologically abnormal tissue has been removed. When the patient is critically ill, limb amputation may be necessary for survival.

In this patient, the skin of the palm and digits was not involved, and the infection extended to the elbow. Complete débridement of the skin and fascia was performed (Fig. 3B and 3C). The extensor tendons were covered with a free microvascular lateral arm flap, and the muscle, exposed up to the elbow, was covered with split-thickness skin grafts (Fig. 3D).

DR. MICHAEL R. FILBIN'S DIAGNOSIS

Necrotizing fasciitis with resulting septic shock.

PATHOLOGICAL DISCUSSION

Dr. Richard L. Kradin: The tissue removed from the right hand and arm shows the variegated appearance of necrotizing fasciitis. At low magnification, focal epidermal vesicle formation can be seen in the skin. The superficial dermis is edematous, but there is little inflammation. However, the deep dermis has a dirty appearance, which is due to extensive, paucicellular, liquefactive necrosis involving the fascial planes and superficial fat of the subcutis (Fig. 4A). Small blood vessels contain patchy intraluminal thrombi (Fig. 4A, inset). Inflammation ranges in areas from mild to marked, with a mixed infiltrate of mononuclear cells and polymorphonuclear neutrophils. Focal abscess formation is present (Fig. 4B). Abundant gram-positive cocci, mostly in chains — a finding that is consistent with the presence of streptococcal species — are seen in areas of necrosis (Fig. 4B, inset). Culture of tissue obtained during the surgical procedure subsequently grew group A streptococci. The histopathological and microbiologic results are diagnostic of necrotizing fasciitis due to infection with group A streptococci.

Necrotizing fasciitis is defined pathologically by necrosis of the deep soft tissue, including fascia, with relative sparing of skeletal muscle. It results in extensive necrosis that often largely spares the overlying skin. This case is typical of necrotizing fasciitis, occurring after a minor skin wound in an otherwise healthy person, with monomicrobial group A streptococcal infection.

GROUP A STREPTOCOCCUS

Dr. Michael R. Wessels: This case illustrates the impressive potential virulence of group A streptococcus in a previously healthy person. This patient had a localized infection at the site of minor trauma, which progressed rapidly to necrotizing fasciitis, involving the entire forearm, and severe systemic manifestations of hypotension, coagulopathy, renal failure, and respiratory insufficiency.

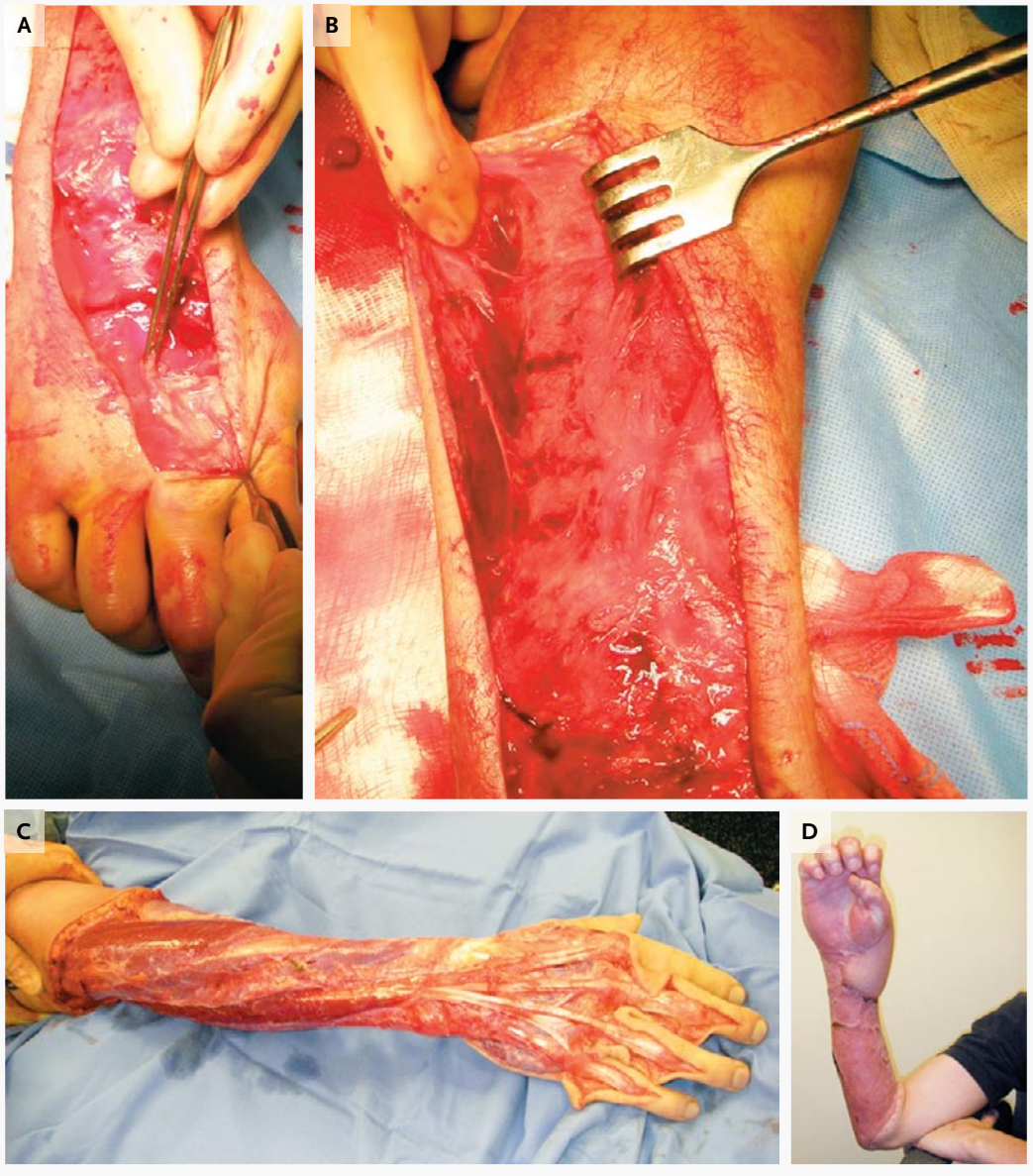

Figure 3. Intraoperative and Follow-Up Clinical Images of the Hand and Arm.

On incision of the dorsum of the right hand, fat necrosis (so-called dishwater pus) was encountered (Panel A). The infection had spread along the fascia to the elbow, with thrombosis of small blood vessels (Panel B). The palmar skin of the hand and the dorsum of the fingertips were spared (Panel C). Four months after skin grafting and free microvascular-flap coverage of the exposed muscle, the patient was back to work and was regaining hand function (Panel D).

NECROTIZING FASCIITIS

In this patient, the portal of entry for the infection that caused necrotizing fasciitis was his right hand. However, the most common presentations of necrotizing fasciitis involve the abdominal wall or perineum, often with polymicrobial infection due to spontaneous, traumatic, or surgical disruption of bowel integrity, particularly in patients with diabetes or immunosuppression. In a patient such as this one, who was healthy and had not recently undergone surgery, monomicrobial infection is the rule, with streptococci or *S. aureus*, including

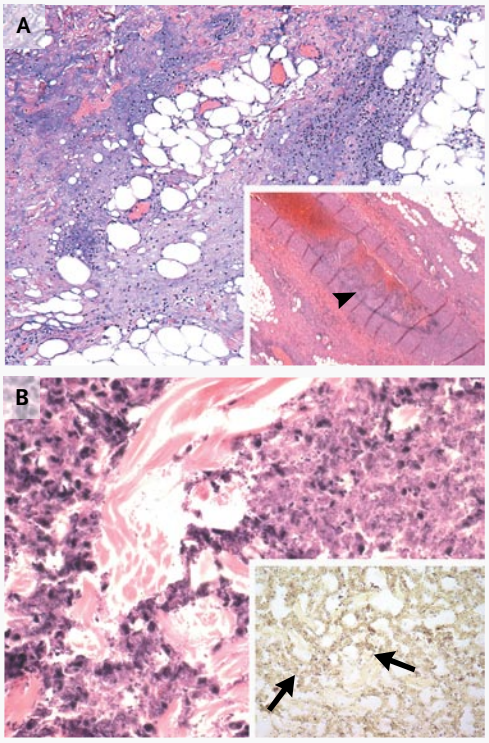

Figure 4. Specimens of Skin and Soft Tissue Removed at the Time of Surgical Exploration.

At low magnification (Panel A, hematoxylin and eosin), extensive bands of liquefactive necrosis and patchy inflammation of the deep dermis and subcutis are evident. A muscular artery (Panel A, inset) contains an eccentric intraluminal thrombus (arrowhead). Focal abscess formation, with numerous degenerating neutrophils, is present in the deep dermis (Panel B, hematoxylin and eosin). Gram's staining of a tissue sample by the Brown and Hopps method shows many gram-positive cocci, mostly in chains, in areas of necrosis (Panel B, inset, arrows).

methicillin-resistant *S. aureus*, implicated most frequently. Necrotizing fasciitis arising as a complication of injection-drug use is often caused by clostridium species, notably *Clostridium sordellii* in association with black-tar heroin.[4,5]

Necrotizing fasciitis is often preceded by a minor injury involving a break in the skin, as it was in this patient. Intact human skin is highly resistant to streptococcal infection. Skin changes are often subtle or absent during the early stages of infection, as they were in this patient. However, severe pain and tenderness of the involved area are typical, and in this case provided an important clue to the diagnosis. Two interesting findings in this case were the absence of frank pus associated with the infected tissue and a relative paucity of neutrophils on histologic evaluation. The latter finding is considered to be an unfavorable prognostic sign in necrotizing fasciitis and may reflect the capacity of group A streptococcus to produce hemolysins and proteases that destroy neutrophils and inhibit their recruitment to the site of infection.[6-12]

STREPTOCOCCAL TOXIC SHOCK SYNDROME

This patient's illness also involved severe systemic manifestations of shock, coagulopathy, and organ failure, a constellation of findings that is consistent with the diagnosis of streptococcal toxic shock syndrome,[13,14] which is associated with a 36% mortality rate — higher than that with any other streptococcal infection syndrome, including necrotizing fasciitis, endocarditis, and meningitis.[15] Most patients infected with an invasive strain of group A streptococcus have an asymptomatic infection or self-limited pharyngitis.[12,13] Why does a life-threatening infection develop occasionally in one person, such as this young man, from the same strain that causes minimal disease in others? For otherwise healthy people, the risk of streptococcal toxic shock syndrome is higher among those with low levels of specific antibodies against the infecting strain and against streptococcal superantigens produced by that strain.[16,17] In addition, specific major-histocompatibility-complex (MHC) class II alleles may have increased affinity for binding group A streptococcus toxins, resulting in an increased release of cytokines, which are thought to be at least in part responsible for the manifestations of the toxic shock syndrome. People in whom these alleles are expressed appear to be at higher risk for the development of streptococcal toxic shock syndrome than do those without the expression of such alleles.[18]

ANTIBIOTIC THERAPY

In a case like this, when group A streptococcus is identified as the sole pathogen, penicillin or another beta-lactam antibiotic can be used. However, the clinical response to penicillin treatment may be slow. Penicillin, which inhibits bacterial cell-wall synthesis, is relatively inactive against bacteria that are no longer rapidly dividing, as may occur after group A streptococci reach a high density in the tissue. Clindamycin, which works independently of the bacterial growth phase, may have the

added benefit of directly inhibiting synthesis of group A streptococcal toxins. I would thus recommend clindamycin as part of the antibiotic regimen for this patient. Although resistance is rare, clindamycin should not be used alone in patients with life-threatening infection until the susceptibility of the isolate has been confirmed.

Intravenous immune globulin has been suggested as adjunctive therapy in patients with the toxic shock syndrome, in order to provide direct neutralization of streptococcal toxins and to exert immunomodulatory effects on T cells. However, no adequately powered, randomized, controlled trial has been completed to establish whether intravenous immunoglobulin is beneficial.[19]

Dr. Ring: The patient was transferred to the intensive care unit, and his condition stabilized within 24 hours. He was treated with penicillin G, clindamycin, vancomycin, and cefepime in the immediate postoperative period; he also received intravenous immune globulin on the first 3 days at the recommendation of infectious-disease consultants. He was discharged home on the 16th hospital day. One month after the final reconstructive surgery, his grafts were healed, and some motility had returned in his fingers. Four months after the procedure, he was back to work as a welder and had recovered nearly complete range of motion in his hand and arm (Fig. 3D).

Dr. Binder: Approximately 3 weeks after the patient's discharge from the hospital, a sore throat developed, and a throat culture obtained at an outside hospital was positive for group A streptococcus. The patient was treated with benzathine penicillin. Approximately 6 weeks after discharge, cellulitis of the right leg developed, which rapidly improved with the administration of vancomycin, clindamycin, and penicillin. At this time, the patient's throat culture was again positive for group A streptococcus. The initial plan was to administer monthly prophylaxis with benzathine penicillin. After receiving several intramuscular injections, the patient declined further injections and has subsequently been treated with oral penicillin, taken twice daily. Since starting penicillin prophylaxis, he has not had any further infections.

Because of these recurrent infections, the patient was evaluated for a possible immunodeficiency. Serum immunoglobulins and total complement levels were normal, except for an IgE level of 1180 IU per milliliter (reference range, 0 to 100). The diagnosis of the hyperimmunoglobulinemia E syndrome was considered, but it was believed that neither the patient's history nor the laboratory findings clearly supported the diagnosis of immunodeficiency.

A Physician: If we lived in an area inhabited by rattlesnakes, this lesion would be very hard to distinguish from a snakebite, with the two puncture wounds on the hand. How would you differentiate these two entities?

Dr. Filbin: It would be difficult to distinguish necrotizing fasciitis from a rattlesnake bite. A bite could cause localized necrosis, erythema, and pain. Although rattlesnakes are not endemic in this area, pets are an important source of rattlesnake bites. The systemic response to a rattlesnake bite results in coagulopathy with disseminated intravascular coagulopathy, as opposed to sepsis and distributive shock. However, a bite wound may lead to necrotizing fasciitis with resulting septic shock.

ANATOMICAL DIAGNOSIS

Necrotizing fasciitis and the toxic shock syndrome, caused by group A streptococcal infection.

Dr. Filbin reports receiving grant support from Biosite for a sepsis biomarker study and serving as an expert witness for litigation involving sepsis. Dr. Ring reports receiving unrestricted research grants from Small Bone Innovations, Smith and Nephew Richards, Wright Medical Technology, Joint Active Systems, Biomet, Medical Modeling, Tornier, and Acumed, receiving consulting fees from Smith and Nephew Richards, Wright Medical, Tornier, and Acumed, receiving royalties from Hand Innovations, and having stock options in Illuminos, MiMedx, and Simplicity Orthopedic Solutions. No other potential conflict of interest relevant to this article was reported.

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