exchange were not clinically effective; gold and cyclophosphamide added sequentially because of treatment failure were also ineffective. Ultimately the patient died with new bullae appearing in previously normal skin and previously healed areas along with crops of blisters. The role of the pemphigus antibody in vivo even when active in tissue cultures in vitro is therefore less certain than is implied in recent studies.[3] Factors other than the antibody, such as certain enzymes,[14] may be important in pathogenesis of this disease.

The role of plasma exchange, used in this case exhaustively over two months, is uncertain. Whereas it has been rapidly successful in other cases,[9-13] it did not prove of clinical benefit in this case. However, this patient failed to respond to any known treatment modality; thus, plasma exchange is not disproved as a possibly successful therapeutic maneuver. The combination of successful antibody removal with lack of clinical success suggests that the mechanism of any benefit found may be more complex than antibody removal. Indeed, the data in this case suggest that when plasma exchange therapy is used, certain markers of disease may lose their clinical value. The procedure can conceivably remove such markers without providing clinical benefit. Thus, clinical benefit that occurs after plasma exchange in many diseases should not be assumed to be due to removal of pathogenic substances.

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Toxic Shock Syndrome Due to Occult Postoperative Wound Infection

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DURING THE past several years, both the public and the medical community have come to know toxic shock syndrome as a potentially lethal symptom complex associated with tampon use in menstruating women. From the first report defining the syndrome,[1] the link with tampon use has been emphasized.[2-13]

There has been debate about whether toxic shock syndrome represents a new disease or merely a significant increase in a formerly unrecognized disease entity.[14] It does bear some similarity to staphylococcal scarlet fever in that both syndromes are associated with staphylococcal bacteria and skin rash formation.[14-20] However, staphylococcal scarlet fever does not cause the remainder of the clinical spectrum of toxic shock syndrome, and it does not show particular association with tampon usage. In fact staphylococcal scarlet fever has been reported in association with a wide range of staphylococcal infections, including empyema, fasciitis, subcutaneous abscess, peritonsillar abscess, mucus membrane colonization and septic abortion.[20]

While attention has been given primarily to tampon usage in association with toxic shock syndrome, recent reports have been published describing nonmenstrual causes.[20-32] Several cases have been associated with postoperative staphylococcal wound infections.[22,24-28]

A striking feature of the postoperative staphylococcal infections resulting in toxic shock syndrome, however, is that signs of local wound infection are rarely present.[8] These patients may present with generalized systemic symptoms, and the fact that a surgical wound infection might be the cause may easily be overlooked. It is therefore crucial that all physicians be aware of the possibility of occult localized infection in patients with symptoms of the syndrome, particularly those in whom a surgical procedure has been done recently. The case presented below illustrates the difficulty this may entail.

Report of a Case

A 35-year-old woman presented to the emergency department with complaint of nausea, vomiting, diarrhea and a rash. Approximately six months earlier she had undergone bilateral augmentation mammoplasty. Over the next few months she noted thinning of the skin over the right implant, which was considered possibly secondary to steroid in the outer lumen of the

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double-lumen prosthetic implant. One week before emergency admission, the right implant was removed and a new one inserted without steroid.

Four days following the revision procedure, the patient noted a sore throat, fever and mild swelling of her hands. The following day diarrhea and a rash developed. Her breasts were examined on the next day; no sign of wound infection was present, but she was started on a regimen of cephadroxil (Duricef). All symptoms continued, however, and a headache developed as well.

She came to the emergency department on the seventh postoperative day, three days after the onset of symptoms. Her menstrual period had begun that morning, and she had inserted a tampon.

On physical examination the patient was conscious but lethargic and there was pronounced tachypnea. Her temperature was 36.9°C (98.4°F) orally and 38.5°C (101.3°F) rectally. The rectal temperature rose to 38.9°C (102°F) several hours later. Pulse rate was 140, respirations 40 and systolic blood pressure 60 mm of mercury measured by Doppler device. A macular erythematous rash was present over the trunk, with vesicles and areas of superficial denudation over the extremities and buttocks. The skin was cool with a generally mottled appearance in addition to the distinct rash. Capillary filling was poor. The neck was supple, and no acute adenopathy was present in the cervical, axillary or inguinal regions. The oral mucosa was significantly dehydrated, but the posterior pharynx was not clearly seen due to an active gag reflex. Conjunctival injection and subconjunctival hemorrhage were present bilaterally. The recent surgical incision overlying the right breast implant was healing well with no sign of infection. Some rales were auscultated over the chest bilaterally, but cardiac examination showed no abnormalities. Bowel sounds were present and the abdomen was mildly tender throughout, but peritoneal signs were absent. On pelvic examination findings were within normal limits except for the presence of a tampon and a small amount of dark vaginal blood. Results of rectal examination were unremarkable; stool specimens were soft, gray and guaiac negative. Neurological findings were within normal limits except that the patient was quite lethargic.

An electrocardiogram showed sinus tachycardia at a rate of 140. On a chest radiograph mild bilateral basilar infiltrates were seen.

Laboratory data were as follows: blood gas findings with the patient breathing room air—pH 7.29, carbon dioxide pressure 19 mm of mercury, oxygen pressure 84 mm of mercury, bicarbonate 9 mEq per liter, carboxyhemoglobin 0.3%; electrolytes—sodium 135, potassium 5.3, bicarbonate 14 and chloride 94 mEq per liter; glucose 55 mg per dl; complete blood count—30,300 leukocytes per μl with 86% total neutrophils, including 54% nonsegmented neutrophils and 6% metamyelocytes, 6% eosinophils, 4% monocytes and 4% lymphocytes. Toxic granulation of the polymorphonuclear leukocytes was noted. Hemoglobin was 14.3 grams per dl and the hematocrit 41.1%. The platelet count was initially 121,000 per μl, but decreased to 14,000 per μl one day after admission. The amylase level was 378 IU per liter and creatinine 6.3 mg per dl. Analysis of urine showed a specific gravity of 1.027, pH 5, 2+ protein, six to nine leukocytes and seven to ten erythrocytes. Prothrombin time was 16.8 seconds with control of 10.5 seconds and activity of 25%.

The recent surgical incision over the right breast was surgically reopened and a small amount of clear serosanguinous material obtained. No organisms were found on Gram's stain, and the specimen was cultured for aerobic and anaerobic organisms.

Cultures were also obtained of specimens from the tampon, cervix, vagina, throat, stool, urine and blood. Catheters were inserted into the peripheral veins, right internal jugular vein and right femoral artery. A Foley urinary catheter was also placed.

Medications included dextrose (25 grams given intravenously), gentamicin (80 mg intramuscularly), methacillin (2 grams intravenously), high-dose steroid (dexamethamethasone, 96 mg intravenously) and an intravenous dopamine infusion in the α-adrenergic range at 15 μg per kg of body weight per minute. After 5 liters of crystalloid intravenous fluid, the central venous pressure was zero and arterial blood pressure by intraarterial monitoring device ranged from 60 to 80 systolic and 30 to 50 mm of mercury diastolic. A repeat chest radiograph showed increasing pulmonary edema, and repeat blood gas studies with 5 liters of inspired oxygen by nasal cannula showed pH 7.24, carbon dioxide pressure 27 mm of mercury, oxygen pressure 56 mm of mercury and bicarbonate 12 mEq per liter.

The patient was transferred from the community hospital emergency department to the intensive care unit of a nearby referral center. The diagnosis was severe infection complicated by shock and adult respiratory distress syndrome. The pattern was considered possibly compatible with toxic shock syndrome.

While there were no local signs of wound infection, and initial reopening of the surgical incision had showed no exudate, the right mammary implant was completely removed in an effort to find the source of infection. Underlying the implant was a collection of 15 to 20 ml of purulent material, which was cultured for aerobic and anaerobic organisms. The left mammary implant was removed as well, but no infection was found. Both wounds were irrigated, packed and allowed to heal by secondary intent.

Coagulase-positive *Staphylococcus aureus* was cultured from the exudate found below the right mammary implant; all other cultures revealed no growth. The patient had been treated empirically with intravenously given nafcillin, which was continued for a ten-day course.

Vascular collapse remained a problem for several days, requiring significant amounts of intravenous fluids as well as α-adrenergic pharmacological agents.

A total of 16 liters of crystalloid fluid was given during the first 36 hours. Support of blood pressure necessitated the simultaneous administration of norepinephrine, epinephrine, dopamine and neosynephrine during the first day, and the continuation of epinephrine and dopamine therapy for an additional two and three days respectively. Mean arterial pressure was initially 55 mm of mercury and stabilized in the 70 to 80 range by the fifth day. Central venous pressure was initially 5 cm of water and never exceeded normal limits.

Significant adult respiratory distress syndrome developed. The patient was intubated and placed on positive pressure ventilation. Positive end-expiratory pressure of 15 cm of water was required to maintain adequate oxygenation. Pulmonary capillary wedge pressure never exceeded 18 cm of water. Bilateral pleural effusions developed and were aspirated, showing sterile transudate. The patient's respiratory status slowly improved and she was extubated on the fifth hospital day.

Maximally abnormal laboratory values were as follows: complete blood count—45,200 leukocytes per μl; hemoglobin 10 grams per dl; 10,000 platelets per μl; fibrin split products between 80 and 160 μg per ml; prothrombin time 11.8 seconds with control of 17.4 seconds and activity of 23%; total bilirubin 8.2 mg per dl with direct bilirubin 5.7 mg per dl; highest unfractionated total bilirubin 9.3 mg per dl; serum aspartate aminotransferase 232 IU per liter; serum alanine aminotransferase 230 IU per liter.

The patient was discharged from hospital 17 days after admission, 20 days following the onset of symptoms and 24 days after the revision augmentation mammoplasty. The breast wounds were still open but granulating well. Several large areas of skin desquamation were present, particularly over the buttocks, but were healing without complication. Trace pitting edema was still detectable at the ankles. She has continued to do well since her hospital stay.

Discussion

The patient obviously had an overwhelming toxic illness accompanied by shock. The source of infection, however, was far from obvious. Symptoms and physical examination findings suggested a respiratory or gastrointestinal tract site. While her history of recent breast operations warranted exclusion of the mammary implant, there was strong evidence against the implant as a source of infection. There were no local signs such as erythema, warmth, tenderness, induration or fluctuance. Even the initial surgical reopening of the incision failed to reveal pus, and Gram's stain and culture of the clear serosanguinous material obtained found nothing remarkable. Only complete removal of the mammary implant revealed the site of infection.

The diagnosis of toxic shock syndrome might have suggested the tampon as an etiologic factor. However, symptoms began three days before the onset of menstruation, and the first tampon had been inserted only on the day of hospital admission.

TABLE 1.—*Definition of Toxic Shock Syndrome**

Fever—temperature $\geq$38.9°C (102°F)

Rash—diffuse macular erythroderma

Desquamation—one to two weeks after onset of illness, particularly of palms and soles

Hypotension—systolic blood pressure $\leq$90 mm Hg for adults or $<$5th percentile by age for children 16 years of age or younger, orthostatic fall in diastolic blood pressure $\geq$15 mm Hg from lying to sitting, orthostatic syncope or orthostatic dizziness

Involvement of at least three of the following organ systems:

- Gastrointestinal—vomiting or diarrhea at onset of illness
- Muscular—severe myalgia or creatinine phosphokinase level $\geq 2\times$ULN
- Mucous membranes—vaginal, oropharyngeal or conjunctival hyperemia
- Renal—blood urea nitrogen or creatinine levels $\geq 2\times$ULN, or $\geq$5 leukocytes per high-power field, in the absence of urinary tract infection
- Hepatic—total bilirubin, serum aspartate aminotransferase or serum alanine aminotransferase levels $>2\times$ULN
- Hematologic—platelets $\leq$100,000 per μl
- Central nervous system—disorientation or alteration in consciousness without focal neurological signs when fever and hypotension are absent

Negative results on the following tests if obtained:

- Blood, throat or cerebrospinal fluid cultures, although blood cultures positive for *Staphylococcus aureus* are accepted by some authors[32]
- Serological tests for Rocky Mountain spotted fever, leptospirosis or rubeola

ULN = upper limit of normal

*Adapted from Morbidity Mortality Weekly Rep.[4,19,32]

Treatment of menstrually related toxic shock syndrome consists of tampon removal and the use of a β-lactamase-resistant antibiotic.[7,33] The latter has been shown to reduce the rate of recurrence of menstrually related toxic shock syndrome.[7] While definitive data are unavailable, the use of a β-lactamase-resistant antibiotic would seem prudent for cases of postoperative toxic shock syndrome as well. The crucial treatment, however, is surgical drainage of the infected site as indicated. Had the source of infection not been identified, it might have seemed reasonable to treat our patient with antibiotics effective against enteric or respiratory tract organisms. However, failure to include a β-lactamase-resistant antibiotic—and failure to drain the infected site—might have been most unfortunate.

The case presented does conform with the criteria suggested by the Centers for Disease Control for toxic shock syndrome (see Table 1).[4,19,34] All four of the mandatory findings were present: fever, rash, desquamation and hypotension. Five of the secondary criteria were present as well: the disease involved the gastrointestinal tract, mucous membranes, kidneys, liver and platelets.

The patient's rash is of particular interest. While it does conform to the Centers for Disease Control criteria of diffuse macular erythroderma and desquamation, the vesicle formation and early denudation are not typical of toxic shock syndrome. They do occur, however, in the scalded skin syndrome, a disease which does not cause the full clinical spectrum found in both

toxic shock syndrome and the case presented. The rash in scalded skin syndrome is caused by the exfoliatin toxin produced by the particular staphylococcal phage type associated with the disease. The staphylococcal organism found in toxic shock syndrome is not known to produce this toxin.[11]

Only one other case of toxic shock syndrome following artificial implant has been reported,[29] and this case also involved a mammary implant. The patient died despite vigorous therapy with antibiotics, fluids and vasopressors and surgical removal of the infected implant.

Postoperative wound infection is a rare cause of toxic shock syndrome, accounting for fewer than 1% of all cases reported to the Centers for Disease Control between January 1, 1980, and July 31, 1981.[29] The truly dangerous aspect is that local wound infection is usually not obvious: signs of local infection were absent in 15 of 17 cases they reviewed.[20] The case reported here was particularly difficult to diagnose; even surgical reopening of the incision at first failed to reveal infection. Wound abscess was discovered only after the implant itself was removed. No physical signs or symptoms of wound infection were ever apparent until this final step was taken.

Conclusion

Local signs of wound infection are typically absent in postoperative toxic shock syndrome. The patient with apparent "flu-type" symptoms may thus present to a primary care or emergency physician rather than to the surgeon. It is crucial, therefore, for all physicians to maintain a high index of suspicion for wound infection in any postoperative patient with fever, rash, hypotension and other symptoms that might easily be dismissed as viral syndrome.

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