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Tularemia is an infectious disease that continues to occur sporadically and in epidemics in the United States. It is characterized as an acute febrile illness with constitutional symptoms associated with skin, glandular, respiratory, or gastrointestinal involvement. Tularemia usually can be treated effectively with streptomycin. Relapse most often occurs when patients are treated with bacteriostatic agents such as chloramphenicol or tetracycline. We present a case of ulceroglandular tularemia distinguished by its relapse after initial streptomycin/doxycycline therapy and subsequent slow response to additional streptomycin. (Henry Ford Hosp Med J 1989;37:73-5)

Tularemia has been recognized since the early 1900s as an infectious disease with diverse manifestations (1). The etiologic agent, *Francisella tularensis*, is a gram-negative coccobacillus that after transmission through tick bite, ingestion, or by aerosol or direct contact with infected animals causes an acute febrile illness associated with skin, glandular, respiratory, or gastrointestinal findings. Rabbits, hares, and ticks are the most common carriers. Tick-borne cases predominate in spring and summer whereas rabbit-associated cases are prevalent in the winter (2). Patients develop one of the following syndromes: ulceroglandular (75% to 85% of cases), glandular (5% to 10%), typhoidal (5% to 15%), or oculoglandular (1% to 2%). Pleuropulmonary complications can occur and may mimic atypical pneumonia similar to that seen with mycoplasma or *Legionella* infections (3). The population at risk includes farmers, sheep shearers, and laboratory workers. There is no known human-to-human transmission. Effective therapy consists of intramuscular streptomycin (4).

We describe a patient with a complicated course of tularemia because of his initial relapse after effective antibiotics and subsequent slow response to repeat therapy. The clinical course prompted consideration for surgical intervention.

Case Report

A previously healthy 43-year-old man was admitted to Henry Ford Hospital in December 1988 complaining of a five-week history of fever, chills, sweats, arthralgias, headaches, and swelling of the left arm. He had spent Thanksgiving in rural South Carolina where he suffered a laceration to his left second finger while cutting raccoon meat one day prior to serving it for the holiday dinner. Three days later, he awoke complaining of generalized arthralgias and developed a severe, persistent occipital headache. About 72 hours later, he noted increased swelling of the medial left arm with tenderness over the epitrochlear and axillary areas. No other family members became ill. Gradually a purulent drainage developed at the laceration site, and he was seen by a local physician who incised and drained the finger and prescribed oral erythromycin. The arthralgias subsided but the cellulitis and constitutional symptoms persisted. Fourteen days after the laceration, he presented to the local emergency room and was admitted for intravenous antibiotic therapy. Treatment consisted of imipenem, 500 mg intravenous piggypack every six hours for days 1 through 8, followed by streptomycin, 500 mg intramuscularly every 12 hours, cefazolin, 2 g intravenous piggypack every eight hours, and doxycycline, 100 mg orally twice daily, for days 9 through 13. His hospital course was complicated by painful adenopathy, especially in the left epitrochlear and axillary areas. Aspiration of the epitrochlear node revealed frank pus which on Gram's stain showed no organisms. Cultures were negative for aerobic, anaerobic, and mycobacterial pathogens.

Serology for tularemia, brucellosis, and toxoplasmosis was also negative at the time of his discharge. Only slight left arm tenderness and swelling remained. Discharge medications included 500 mg of oral cephalexin every eight hours and 100 mg of doxycycline twice daily until completion of ten days of therapy for suspected tularemia. He returned to the Detroit area. Nine days after discharge he experienced a recurrence of symptoms while still on antibiotic therapy. Symptoms included increased left arm swelling and tenderness, headache, nausea, and fever. He did not have any symptoms of cough, diarrhea, and abdominal or chest pain. He presented to the Henry Ford Hospital emergency room four days later with a temperature of 38.9°C (102°F), pulse of 80 beats/min, blood pressure of 122/78 mm Hg, and respiration of 16 breaths/min. The patient was alert and oriented but appeared in moderate distress, splinting his left arm to his abdomen. A 2 x 4 cm area of cellulitis and swelling was noted over the left epitrochlear area (Fig 1). There was also a 4 x 5 cm area of induration and erythema in the left axilla that was exquisitely tender to touch (Fig 2). Fluctuance, ulceration, lymphadenitis, and drainage were not noted. A ½ cm healed lac-

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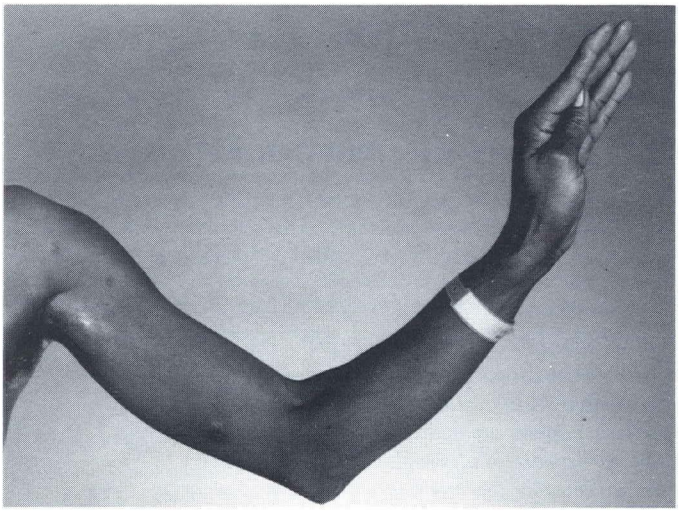

Fig 1—Ulceroglandular tularemia with epitrochlear and axillary adenitis.

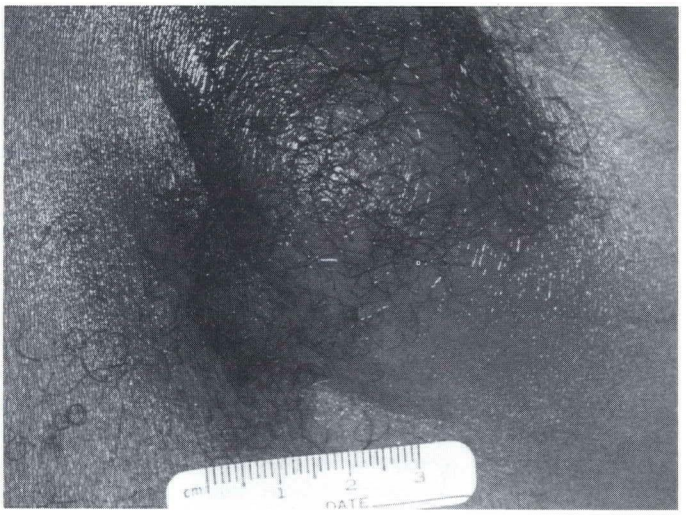

Fig 2—View of the axillary swelling and cellulitis.

eration was present at the distal medial second finger with surrounding purple discoloration. The rest of the physical examination was unremarkable.

WBC count was 19.2 10^9/L (19,200/μL) with 0.48 (48%) neutrophils, 0.06 (6%) bands, 0.34 (34%) lymphocytes, and 0.07 (7%) monocytes. His hemoglobin was 123 g/L (12.3 g/dL), creatinine 106 μmol/L (1.2 mg/dL), and ESR 79 mm/h. Monospot and hepatitis B surface antigen tests were negative. Liver function test results were mildly elevated with an aspartate aminotransferase of 1.15 μkat/L (69 U/L), alanine aminotransferase of 1.53 μkat/L (92 U/L), alkaline phosphatase of 2.1 μkat/L (126 U/L), and gamma-glutamyltransferase of 1.72 μkat/L (103 U/L). Chest roentgenogram was negative. A needle aspirate of the left epitrochlear area revealed on Gram's stain numerous "questionable" gram-negative bacilli.

After routine cultures of sputum, blood, and urine were obtained, he was started on cefazolin, 1 g intravenous piggypack every eight hours, and streptomycin, 500 mg intramuscularly every 12 hours. The nodal aspirate was sent for aerobic, anaerobic, fungal, and mycobacterial cultures. An ultrasound of the left axilla was negative for abscess. Within 24 hours, his left arm pain subsided. The fever, headache, and arthralgias decreased over the next three days. Swelling and cellulitis improved slowly over the following week. Due to the sluggish response, lymph node excision was discussed but abandoned. Streptomycin therapy was continued for 14 days total (four days on an outpatient basis). After antibiotic therapy was discontinued, he continued to improve slowly and was asymptomatic at follow-up two months later.

Serologic evaluation revealed agglutination antibodies to *Francisella tularensis* positive at a dilution of 1:320. Titers to *Brucella abortus* were less than 20, *Proteus* Ox-19 antigen 1:160, and toxoplasmosis less than 8. Fungal, mycobacterial, and routine cultures of the nodal aspirate were negative.

Discussion

Our patient manifested the ulceroglandular form of tularemia with inoculation occurring from a laceration rather than a tick bite. The prominent epitrocheal and axillary lymphadenopathy proximal to the inoculation site and constitutional symptoms were classic presentations (5). Skin exposure, rather than ingestion, was the probable mode of transmission since none of the family members became ill and gastrointestinal symptoms were absent.

Our patient fulfilled the criteria for the ulcer-node syndrome. The differential diagnosis includes rat-bite fever (6), *Pasteurella* (7), cat-scratch disease (8), *Mycobacterium marinum* (9), nocardiosis (10), sporotrichosis (11), cutaneous anthrax (12), *Erysipelothrix* (13), tularemia (5), staphylococcal or streptococcal lymphangitis (14), brucellosis (15), *Listeria* (16), syphilis (17), lymphogranuloma venereum (18), scrub typhus (19), or plague (20). He denied any history of animal bite or scratch, contaminated percutaneous inoculation, sexually transmitted diseases, tick bites, or exposure to sick animals or their hides, gardening, or fish tanks. The history of cutaneous exposure while cleaning raccoon meat with subsequent ulcer formation and lymphadenitis strongly suggested the diagnosis of tularemia.

The diagnosis of tularemia is usually confirmed by serologic testing. It is not surprising that bacterial agglutinins were initially absent in our patient. In a study of 65 patients, Evans et al (5) demonstrated that 14 days after inoculation no patient had a diagnostic agglutinin titer ($\geq$ 160) before the 11th day and that all but two were in the diagnostic range by the 16th day. Perhaps prior therapy with erythromycin, which has been shown to be effective in treating tularemia (21,22), blunted the serologic response in our patient.

Patients with brucellosis may have elevations in their tularemia titers (23). Our patient had a *Brucella* titer of less than 20 and a *Proteus* Ox-19 antigen of 1:160. Serologic cross-reactivity with *Proteus* Ox-19 antigen is uncommon but has been described (24).

The initial favorable response followed by relapse is seen in 20% of patients treated with bacteriostatic agents such as chloramphenicol and tetracycline but is rarely seen in patients treated with streptomycin (25,26). Our patient's relapse most

likely can be attributed to only partial treatment with streptomycin and completion of therapy with doxycycline.

The drug of choice is intramuscular streptomycin, 15 to 20 mg/kg/day in divided doses for seven to ten days. Relapse after treatment with streptomycin is rare, but when it occurs it should be followed by a repeat 14-day course of streptomycin. While response is usually rapid, it can be slow, especially if the patient delays initial treatment (5). Surgical excision of infected nodes is not indicated and may be associated with dissemination of disease or fistula formation. Fluctuant areas of abscess formation should be drained to facilitate a rapid clinical response.

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