Typhoidal Tularemia The typhoidal presentation is now considered rare in the United States. The source of infection in typhoidal tularemia is usually associated with pharyngeal and/or gastrointestinal inoculation or bacteremic disease. Fever usually develops without apparent skin lesions or lymphadenopathy. Some patients have cervical and mesenteric lymphadenopathy. In the absence of a history of possible contact with a vector, diagnosis can be extremely difficult. Blood cultures may be positive and patients may present with classic sepsis or septic shock in this acute systemic form of the infection. Typhoidal tularemia is usually associated with a huge inoculum or with a preexisting compromising condition. High continuous fevers, signs of sepsis, and severe headache are common. The patient may be delirious and may develop prostration and shock. If presumptive antibiotic therapy in culture-negative cases does not include an aminoglycoside, the estimated mortality rate is relatively high.

Other Manifestations *F. tularensis* infection has been associated with meningitis, pericarditis, hepatitis, peritonitis, endocarditis, osteomyelitis, and sepsis and septic shock with rhabdomyolysis and acute renal failure. In cases of tularemia meningitis, a mean white blood cell count of 1788/μL, a predominantly mononuclear cell response (70–100%), a depressed glucose level, an elevated protein concentration, and a negative Gram's stain are typically found on examination of cerebrospinal fluid.

DIFFERENTIAL DIAGNOSIS

When patients in endemic areas present with fever, chronic ulcerative skin lesions, and large tender lymph nodes (Fig. 195-1), a diagnosis of tularemia should be made presumptively, and confirmatory diagnostic testing and appropriate therapy should be undertaken. When the possibility of tularemia is considered in a nonendemic area, an attempt should be made to identify contact with a potential animal vector. The level of suspicion should be especially high in hunters, trappers, game wardens, professional landscapers, veterinarians, laboratory workers, and individuals exposed to an insect or another animal vector. However, up to 40% of patients with tularemia have no known history of epidemiologic contact with an animal vector.

The characteristic presentation of ulceroglandular tularemia does not pose a diagnostic problem, but a less classic progression of regional lymphadenopathy or glandular tularemia must be differentiated from other diseases (Table 195-3). The skin lesion of tularemia may resemble those seen in various other diseases but is generally accompanied by more impressive regional lymphadenopathy. In children, the differentiation of tularemia from cat-scratch disease is made more difficult by the chronic papulovesicular lesion associated with *Bartonella henselae* infection (Chap. 197). Oropharyngeal tularemia can resemble and must be differentiated from pharyngitis due to other bacteria or viruses. Pulmonary tularemia may resemble any atypical pneumonia. Typhoidal tularemia and tularemia meningitis may resemble a variety of other infections.

LABORATORY DIAGNOSIS

The diagnosis of tularemia is most frequently confirmed by agglutination testing. Microagglutination and tube agglutination are the techniques most commonly used to detect antibody to *F. tularensis*. In the standard tube agglutination test, a single titer of ≥1:160 is interpreted as a presumptive positive result. A fourfold increase in titer between paired serum samples collected 2–3 weeks apart is considered diagnostic. False-negative serologic responses are obtained early in infection; up to 30% of patients infected for 3 weeks have sera that test negative. Late in infection, titers into the thousands are common, and titers of 1:20–1:80 may persist for years. Enzyme-linked immunosorbent assays have proved useful for the detection of both antibodies and antigens.

Culture and isolation of *F. tularensis* are difficult. In one study, the organism was isolated in only 10% of more than 1000 human cases, 84% of which were confirmed by serology. The medium of choice is cysteine-glucose-blood agar. *F. tularensis* can be isolated directly from infected ulcer scrapings, lymph node biopsy specimens, gastric washings, sputum, and blood cultures. Colonies are blue-gray, round, smooth, and slightly mucoid. On media containing blood, a small zone of α hemolysis usually surrounds the colony. Slide agglutination tests or direct fluorescent antibody tests with commercially available antisera can be applied directly to culture suspensions for identification. Most clinical laboratories will not attempt to culture *F. tularensis* because of the infectivity of the organism from the culture media and the consequent risk of a laboratory-acquired infection. Although tularemia is not spread from person to person, the organism can be inhaled from culture plates and infect unsuspecting laboratory workers. In most clinical laboratories, biosafety level 2 practices are recommended to handle clinical specimens thought to contain *F. tularensis*; however, biosafety level 3 conditions are required for procedures that produce aerosols or droplets during manipulation of cultures containing or possibly containing this organism.

A variety of polymerase chain reaction (PCR) methods have been used to detect *F. tularensis* DNA in many clinical specimens but mostly in ulceroglandular disease. The majority of these methods target the genes encoding outer-membrane proteins (e.g., *fopA* or *tul4*). A 16S rDNA sequence identification PCR may be helpful when the patient's clinical information does not lead the clinician to suspect a diagnosis of tularemia.

TREATMENT TULAREMIA

Only aminoglycosides, tetracyclines, chloramphenicol, and rifampin are currently approved by the U.S. Food and Drug Administration for the treatment of tularemia. Gentamicin is considered the drug of choice for both adults and children. The dosage for adults and children is 5 mg/kg daily in two divided doses. Gentamicin therapy is typically continued for 7–10 days; however, in mild to moderate

TABLE 195-3 TULAREMIA: DIFFERENTIAL DIAGNOSIS, BY CLINICAL DISEASE CATEGORY

Glandular	Oropharyngeal	Typhoidal	Pulmonary
Pyogenic bacterial infection[a]	Group A streptococcal pharyngitis	Typhoid fever	*Mycoplasma pneumoniae* pneumonia
Nontuberculous mycobacterial infection	*Arcanobacterium haemolyticum* pharyngitis	Other *Salmonella* bacteremias	*Chlamydia pneumoniae* pneumonia
Sporotrichosis	Diphtheria	Rocky Mountain spotted fever	Psittacosis
Tuberculosis	Infectious mononucleosis	Human monocytotropic ehrlichiosis	*Legionella pneumophila* pneumonia
Syphilis	Various viral infections[b]	Human granulocytotropic anaplasmosis	Q fever
Anthrax		Infectious mononucleosis	Histoplasmosis
Rat-bite fever		Brucellosis	Blastomycosis
Scrub typhus		Toxoplasmosis	Coccidioidomycosis
Plague		Tuberculosis	Various viral infections[d]
Lymphogranuloma venereum		Sarcoidosis	
Cat-scratch disease		Malignancy[c]	

[a]*Staphylococcus aureus, Streptococcus pyogenes.* [b]Adenovirus, enteroviruses, parainfluenza virus, influenza viruses A and B, respiratory syncytial virus. [c]Hematologic and reticuloendothelial malignancies. [d]Influenza viruses A and B, parainfluenza virus, respiratory syncytial virus, adenovirus, enteroviruses, hantavirus.