Case Report: Atypical Cutaneous Manifestations of Tularemia after Horsefly Bite

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Abstract. Tularemia is an infectious zoonosis caused by *Francisella tularensis*, an aerobic, noncapsulated, Gram-negative coccobacillus. It is more common in the northern hemisphere, and there are sporadic reports in non-endemic areas. The bacterium is usually transmitted by the bite or feces of a tick or other arthropods such as mosquitoes and horseflies. We report a case of an Italian patient with tularemia after a horsefly bite.

CASE REPORT

A 48-year-old woman was admitted to our Department of Dermatology for the onset of a rapidly enlarging itchy erythematous papule on her shoulder. The patient referred a horsefly bite on the site of the lesion during a horseback trip 2 days before. Despite skin manifestation, she was asymptomatic and denied any drug intake. At the first visit, she presented an erythematous nodular lesion surrounded by an inflammatory area with poorly defined borders (Figure 1) and complained of pruritus and pain on palpation. Physical examination showed cervical, supraclavicular, and axillary painful palpable lymph nodes. Five days later, she became febrile (38.5°C) with headache, chills, arthralgias, myalgias, headache, and asthenia, developing a diffuse non-itchy maculopapular exanthem on the trunk and limbs, making a differential diagnosis difficult for its atypical cutaneous presentation. Laboratory tests performed at that time showed leukocytosis ($12.500 \times 10^6/L$) with lymphocytosis (42%). Urinalysis was normal. Serology for Epstein–Barr virus; cytomegalovirus; Hepatitis A, B, and C viruses; *Brucella*; and *Rickettsia* were negative or indicative of past immunity. The patient was treated with amoxicillin and clavulanic acid (875/125 mg) every 12 hours for a week, but the constitutional symptoms and the clinical picture remain unchanged. At the end of the treatment, the patient was tested for antibodies anti-*Francisella tularensis* using the latex agglutination assay, showing a titer of 1/512. Positive anti-*F. tularensis* ELISA immunoglobulin M (IgM) (optical density [OD] value 1,285) and immunoglobulin G (IgG) (OD value 1,975) antibodies (Institut Virion\Serion, Würzburg, Germany) confirmed the diagnosis of tularemia. Afterward, the patient started systemic treatment with antibiotics (ciprofloxacin 500 g three times daily for 7 days and gentamicin 2 mg/kg/i.m. three times daily for 5 days). The systemic symptoms improved after 5 days of treatment, with complete clinical resolution in about 10 days. After 1 month, lymphadenopathy completely resolved without suppuration and serology showed a decrease in IgG antibody titers (1/128) and was IgM negative.

DISCUSSION

Francisella tularensis causes an acute, febrile infectious zoonosis and is transmitted by the bite or feces of a tick or other arthropods such as mosquitoes and horseflies.¹

Furthermore, it can be transmitted from skin contact with infected animals such as rabbits, muskrats, beavers, sheep, amphibians, and fish, acting only as mechanical vectors.^{2,3} However, in up to 40% of patients, no history of epidemiologic contact with an animal or arthropod vector can be identified. It has been rarely associated with infected water or food. Following inoculation into the skin, the bacteria multiply locally and after 2–5 days cause an erythematous itchy papule that rapidly enlarges, usually forming an ulcer. They then spread to regional lymph nodes producing lymphadenopathy that may become fluctuant and even discharging. Systemic diffusion through blood may occur and affected organs show areas of necrosis with granuloma formation. Infection of the eye may occur by conjunctiva and inhalation of the bacterium may result in pneumonia. The diagnosis of tularemia is generally based on symptoms and patient history,

FIGURE 1. Erythematous papulo-nodular skin lesion on the site of the horsefly bite. This figure appears in color at www.ajtmh.org.

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imaging, and laboratory investigations. In our patient, the history of a horsefly bite, the clinical symptoms, and laboratory investigations allowed us a prompt diagnosis and treatment. Different clinical types of tularemia, such as oropharyngeal, ulceroglandular, oculoglandular, typhoidal, and pulmonary type, have been described. Skin symptoms may develop after infection in all tularemia types, probably in response to systemic bacterial spreading.^{4,5} The cutaneous findings may be divided into those of primary lesions (ulcerations at the point of entry) and secondary lesions.⁶ The latter lesions may be papular, maculopapular, vesicular, or pustular eruptions; erythema nodosum; and vasculitis-like or phototoxic eruptions.⁷ About 20% of patients with tularemia have a rash, which may begin as a macular or maculopapular eruption and may progress to a pustular pattern. In our case, the patient had an uncommon autochthonous form of tularemia presenting with skin involvement without ulcer formation, lymphadenopathy, fever, and systemic symptoms, recalling the typhoidal form. As with many other tick-borne diseases, tularemia may, early in its course, have a nonspecific presentation. Moreover, many individuals may not be aware of or recall having been bitten by a tick or fly. Therefore, the history of the patient is crucial, including travels, work, and animal and arthropod exposure. Tularemia has a broad geographical distribution, and there is evidence of local emergence or reemergence of the disease in Europe.⁸ At the international level (World Organization for Animal Health, Office International Des Epizooties), the notification is only mandatory when a new disease event occurs in a country; however, when a disease is endemic in a country, there is no longer any obligation to declare it. For this reason, probably, the incidence of tularemia may not be an accurate reflection of the extent of this disease. In Italy, the incidence of tularemia seems to be underestimated. National data on mortality and morbidity (obtained by the National Institute of Statistics; ISTAT) and data concerning hospitalizations for tularemia (obtained by the National Hospital Discharge Database) from 1979 to 2010 reported 474 cases and no deaths (ISTAT).⁹ Furthermore, the epidemiological study of D'Alessandro et al.⁹ demonstrates a wide underreporting of the disease. Probably, similar situations are also present in adjacent countries. There are some reports of tularemia in high-altitude regions such as the Swiss Alps.¹⁰ The epidemiology in France is slightly different, where tularemia is endemic but rare. In one study analyzing a 5-year period (2006–2010), 18.8% of the French patients presented with pulmonary type on hospitalization, showing that tularemia is more severe than usually thought in Western Europe.¹¹ In fact, delayed diagnosis and late administration of effective antibiotic treatment may result in increased morbidity and a greater risk of mortality for infected patients. The Centers for Disease Control and Prevention (CDC) guidelines recommend the use of the following antibiotics to treat tularemia: streptomycin, gentamicin, doxycycline, and ciprofloxacin. The duration of treatment usually depends on the stage of the

disease and CDC guidelines indicate that it may be last for 10–21 days.¹² In our case, the patient was successfully treated with the association of ciprofloxacin and gentamicin, both active against *F. tularensis*, and she achieved complete resolution of her symptoms in only 10 days. In some cases of tularemia, such as patients receiving anti-tumor necrosis factor treatment, that manifest severe glandular type of tularemia, prolonged treatment with doxycycline–ciprofloxacin may be required because of the possible relapse.¹³

It is important to understand the epidemiology of tularemia and to recognize promptly cutaneous manifestations to reduce the risk of morbidity and mortality in infected patients.

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