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Separating the chaff from the grain (Tularemia)

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Abstract. – A case of ulcero-glandular tularemia is presented. Discussion is based on the differential diagnosis of a patient presenting with cutaneous lesions, regional lymphadenopathy and fever.

Key Words:

Tularemia, Cat scratch disease, Cutaneous anthrax.

Case

A 56 year old woman presented with fevers, chills, dry cough, headaches and body aches of 5 days duration preceded by a skin lesion on her right elbow and followed by diarrhea and vomiting. She suffered from ulcerative colitis. Carcinoid tumor of the terminal ileum was diagnosed 2 months ago. Her medications included amitriptyline, mesalamine, ropinirole and finasteride. She did not smoke or use illicit drugs and drank alcohol socially. She kept a dog and was scratched by her son`s cat few weeks ago but had no history of exposure to other animals, ticks or fleas. She did not hunt or farm and had not been to a forest recently.

Her temperature was 40.9°C, blood pressure 118/73 mmHg, pulse rate 85/minute, and respiratory rate 18/minute. A 1.5×2.0 cm, tender, erythematous, ulcerated, papular lesion with raised edges was seen on the extensor surface of her right elbow (Figure 1). Tender lymphadenopathy without lymphangitis was noticed in the right axilla. Spleen and liver were not palpable but Castell's sign was positive. Rest of the physical examination was unremarkable. Levels of urea, creatinine, electrolytes, alkaline phosphatase, bilirubin and total protein were normal on admission. Hemoglobin was 114 g/L (120-160), white cell count 1.6×10^9/L (4.1-10.0), neutrophils 1.0×10^9/L (1.5-6.5), lymphocytes 0.4×10^9/L (1.2-3.4), and platelets 55×10^9/L (150-400). Alanine aminotransferase (ALT) was 60U/L (4-55), and albumin 31 g/L (35-50). Chest X-Ray showed mild bibasilar patchy atelectasis. Computerized tomographic scan (CT scan) of the chest showed right axillary lymphadenopathy, the largest node measuring 2.4 cm, but no evidence of hilar or mediastinal lymphadenopathy. Small bilateral pleural effusions were noted but lungs were clear otherwise. The spleen was enlarged with a maximum longitudinal measurement of 14.8 cm on abdominal ultrasound.

Mesalamine was discontinued. Specimens of urine, stool and blood were obtained for culture but remained negative. Treatment with intravenous ceftriaxone was begun. Chills and diarrhea persisted and she continued to spike fever up to 38.1°C. On the 4th hospital day ceftriaxone was replaced by intravenous piperacillin-tazobactam. Serological tests for *Cytomegalovirus*, Lyme disease, *Mycoplasma pneumoniae*, *Parvovirus B19*, *Epstein Barr virus*, *Coxiella burnetti*, *Rickettsia*, *Bacillus anthracis*, *Bartonella henselae* and *Francisella tularensis* were sent. Antinuclear antibodies were positive at a titer of 1:2560. Antineutrophil cytoplasmic antibody (ANCA) was positive with a perinuclear staining pattern. Myeloperoxidase (MPO-ANCA) was 7 U/ml (0-6) and proteinase 3 (PR3-ANCA) was 21 u/ml (0-6).

Right axillary lymph node biopsy showed a predominantly T-cell population with no evidence of non-Hodgkin's B-cell lymphoma. A bone marrow biopsy showed normocellular marrow with mild granulocytic hyperplasia. Skin biopsy from the elbow lesion revealed granulomatous inflammation. Cultures of the biopsy specimen did not grow any organisms and PAS and Ziehl-Neelsen stains failed to show any evidence of fungal or tuberculous infection.

Temperature continued to spike and oral doxycycline was added on day 5 of hospital admission. High fever and chills developed on day 6. Temperature normalized on day 7 and remained so. Results of some serological tests were received (Table I). She was discharged home on oral doxycycline.

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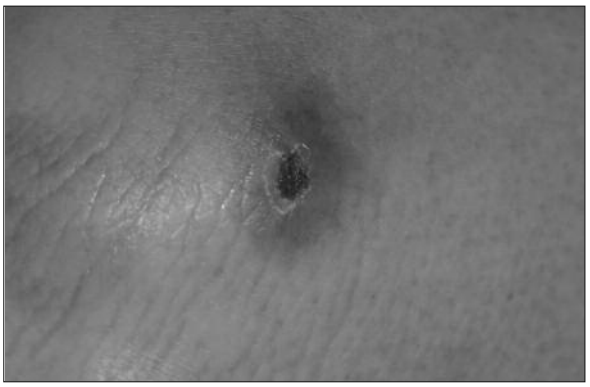

Figure 1. Eschar of Ulceroglandular tularemia.

At follow up 6 weeks later she felt fatigued but had no fevers, chills or diarrhea. Skin lesion had healed without scarring and lymphadenopathy had resolved. Results of the serological tests for Bartonella, Coxiella and Tularemia were received (Tables II and III).

Differential Diagnosis

The patient's initial presentation is consistent with an infective process. Diarrhea may be due to viral or bacterial gastroenteritis, a flare up of ulcerative colitis or may be related to carcinoid tumor. The differential diagnosis of a cutaneous ulcerative lesion with regional lymphadenopathy and fever includes bacterial, viral, fungal and atypical mycobacterial infections. The differential diagnosis of fever, pancytopenia, and nonspecific constitutional symptoms is wide and includes neoplasms, autoimmune diseases, granulomatous diseases and infections. Lymphomas and other lymphoproliferative disorders are important considerations but are usually associated with generalized lymphadenopathy and hepatosplenomegaly. Lymph node and bone marrow biopsy results exclude these disorders. *Mycoses*, *atypical mycobacteria*, *Bartonella henselae* and *F. tularensis* can cause granulomatous inflammation. Differential diagnosis of lymphocutaneous lesion, fever and splenomegaly is wide and include Lyme disease, rickettsial diseases, cat-scratch disease, anthrax, and tularemia, fungal, viral and atypical mycobacterial infections. Infection due to *Blastomyces dermatitidis*, *Histoplasma capsulatum* and *Coccidiodes immitis* is unlikely as they cause multiple cutaneous nodules and generalized lymphadenopathy rather than a single nodule and focal lymphadenopathy. Moreover, there is no history of travel to mycoses endemic areas. *Sporothrix schenckii* is common in soil and on plant materials and usually causes infection by contamination of a wound resulting in a cutaneous lesion but nodular lymphangitis would be expected rather than focal lymphadenitis. *Cryptococcus neoformans* is transmitted by pigeons and associated with a cutaneous lesion and sporotrichoid lymphadenitis. There is no history of exposure to pigeons and therefore is unlikely[1]. Mycobacterial diseases, particularly due to *Mycobacterium chelonae*, *Mycobacterium fortuitum*, and *Mycobacterium marinum* can cause lymphocutaneous disease. *Mycobacterium marinum* is transmitted through

Table I.

Cytomegalovirus IgM	Negative
Cytomegalovirus IgG	Present
Lyme IgG/M Total antibody	Absent
Mycoplasma pneumonia IgM	Negative
Parvovirus B19 IgM	Negative
Epstein Barr virus VCA IgM	Negative

Table II.

Antigen		Acute	Convalescent
Coxiella burnetti IFA			
	IgM	Negative	Negative
Phase I	IgG	< 1:32	< 1:32
Phase II	IgG	< 1:32	< 1:32
Rickettsia rickettsii IFA	IgG	< 1:32	< 1:32
Rickettsia typhi IFA	IgG	< 1:32	< 1:32
Bartonella Henselae IFA	IgG	< 1:64	< 1:64
Francisella tularensis			
Microagglutination test		1:32	1:1024

swimming pools or fresh and salt water lakes and causes nodular lymphadenitis. Our patient did not have any risk factors for mycobacterial diseases and cultures of the biopsy specimen did not grow any organisms and PAS and Ziehl-Neelsen stains were negative for fungal or tuberculous infection.

Orthopoxvirus and *Parapoxvirus* cause cutaneous lesions with regional lymphadenopathy. *Orthopoxvirus* causes cowpox and is associated with contact with a cow, rodent, or a cat. *Parapoxvirus* causes orf and is associated with contact with a sheep or a goat. Our patient had no history of contact with cow, sheep or goat. *Rhodococcus equi* may cause a nodular lesion with ipsilateral adenopathy but the organism is transmitted by contact with horses and soil contaminated with horse manure and there is no such history in our patient[2]. *Nocardia* species are found in soil and water and may cause lymphocutaneous nocardiosis[3]. *Yersinia pestis* can cause bubonic plague with tender lymphadenopathy but there is usually no cutaneous lesion and the course would be fulminant unlike in our patient. Cats can transmit *Pasteurella multocida* but this infection usually causes a rapidly spreading cellulitis.

Cat-scratch disease due to *Bartonella henselae* infection, cutaneous anthrax due to *Bacillus anthracis*, and ulceroglandular tularemia due to *Francisella tularensis* are at the top of differential diagnosis. The most common manifestation of cat scratch disease is axillary lymphadenopathy and an antecedent cutaneous inoculation lesion of the hand or arm[4]. The lesion typically begins as a papule, then becomes vesicular and ulcerates. There is associated regional lymphadenopathy, which may suppurate and drain and can persist for many months. Nodular lymphangitis is rare. Low grade fever and prolonged constitutional symptoms are common.

Cutaneous anthrax is typically a painless, pruritic, popular or vesicular lesion filled with a clear or serosanguineous fluid containing numerous Gram-positive bacilli. The vesicle ruptures and forms an eschar with surrounding gelatinous, non-pitting edema and smaller vesicles. Regional lymphadenopathy may be present. Low grade fever and malaise are common[5]. Negative blood cultures and Gram stain smear of the ulcer makes anthrax unlikely in our patient. Moreover, Anthrax is not known to cause granulomas.

Development of high fever and chills on day 6 of admission after doxycycline was initiated probably represented Jarisch-Herxheimer reaction which occurs most commonly in the treatment of secondary syphilis, toxoplasmosis, louse- and tick-borne relapsing fevers, bartonellosis and tularemia.

A presumptive diagnosis of cat scratch disease can be made by demonstrating the *B. henselae* bacilli with the use of Warthin-Starry silver impregnation staining on histological specimen. *B. henselae* can also be cultured from blood, lymph nodes, and other tissues but grows slowly and, therefore, requires a 6-week incubation period. Serologic testing for the presence of antibodies to *B. henselae* is the most widely used test to confirm the diagnosis of cat scratch disease[6]. In our patient, Warthin-Starry silver impregnation staining of the tissues from the ulcer and lymph nodes did not show any *Bartonella* species and serology was negative.

Ulceroglandular tularemia was diagnosed on the basis of serological tests. Tularemia usually causes leukocytosis whilst platelets and differential counts are usually normal. In our patient leucocytes and platelets returned to normal values after the cessation of mesalamine, indicating mesalamine was the cause of leucopenia and thrombocytopenia.

Commentary

Experienced physicians are able to interpret the data in the light of coexisting disorders since the laboratory results may be misleading if a coexisting disease and not the underlying condition is responsible for the abnormal values. Leukocytosis rather than leukopenia would be expected in tularemia and thrombocytopenia is not a feature of tularemia. Both ulcerative colitis and mesalamine may cause leucopenia and thrombocytopenia. These findings in our patient could have easily misdirected the physician. Similarly, positive test results for antinuclear and antineutrophil cytoplasmic antibodies could have led to the wrong diagnosis. ANA and ANCA have been reported to be present in inflammatory bowel disease. Most often the ANCA staining pattern is of the perinuclear type (p-ANCA), although nuclear and cytoplasmic staining is also seen[7,8]. To separate the chaff from the grain as well as looking beyond the obvious is an important quality of an astute physician.

Tularemia is caused by a gram negative bacillus *Francisella tularensis.* The incidence of the disease has declined from a peak of 2300 cases reported in 1939 to 142 cases reported in 2000 in

the US[9]. Although distributed worldwide, tularemia occurs primarily in the northern hemisphere from approximately 30° to 70° north latitude[10]. There are two types of *F. tularensis*. Type A is predominantly found in United States and Canada and causes more severe disease than type B, which is predominantly found in Europe and Asia. *Francisella tularensis* is transmitted by arthropod bite (deerflies, ticks, mosquitoes or fleas), contact with blood or tissue of infected animals, ingestion of contaminated water or meat or inhalation of aerosols. Animals, typically rabbits, but also squirrels, beavers, muskrats, rodents and other small animals are reservoirs of infection. Transmission has been reported in individuals sustaining hamstring and cat bites[11]. Outbreaks have also been associated with use of lawn mowers and brush cutters. In the United States, ticks and biting fleas are the most important vectors of transmission whilst mosquitoes transmit the infection in Europe[12]. Laboratory workers, landscapers, farmers, veterinarians, hunters, trappers, cooks and meat handlers are at increased risk of acquiring infection.

Six clinical syndromes are recognized depending on the route of infection. In ulceroglandular variety, the cutaneous lesion begins as a papule which ulcerates with raised edges and forms an eschar and is usually associated with regional lymphadenopathy. Unlike anthrax the cutaneous lesion is painful. Like cat-scratch disease involved lymph nodes may suppurate and drain and there is no associated lymphangitis. Fever, chills, malaise, myalgia, arthralgia, sore throat and fatigue are common symptoms. Oculoglandular tularemia is characterized by painful, purulent unilateral conjunctivitis with cervical and periauricular lymphadenopathy. Painful periauricular lymphadenopathy is unique for tularemia and differentiates oculoglandular tularemia from cat-scratch disease, tuberculosis, sporotrichosis and syphilis[13]. Ingestion of infected food or water may cause oropharyngeal or gastrointestinal tularemia. Oropharyngeal tularemia is characterized by acute exudative pharyngitis, tonsillitis or stomatitis with cervical lymphadenopathy. Tonsils may be covered by a yellow or white pseudomembrane. Abdominal pain, nausea, vomiting diarrhea, gastrointestinal bleeding and mesenteric lymphadenopathy characterize gastrointestinal tularemia. Typhoidal tularemia has symptoms of fever, chills, dry cough, myalgia, arthralgia and sore throat without any focal signs. Inhalation of the aerosolized organisms causes pneumonic tularemia. Symptoms include fever, non-productive cough, pleuritic chest pain and dyspnea. Chest X-ray will show pulmonary infiltrates which may be bilateral and associated with hilar adenopathy.

The laboratory diagnosis of tularemia can be challenging. History of exposure to ticks or fleas is absent in a significant proportion of cases. Diagnosis of tularemia can be confirmed by serological tests but antibody titers take about a week to become positive. The finding of a single titer of more than 1:128 with microagglutination studies or more than 1:160 with agglutination studies is a strong evidence of recent or past infection. A four-fold or greater titer rise in two samples taken two weeks apart is confirmatory evidence of recent infection. Detectable antibodies persist for many years after a bout of tularemia[14]. Culture of blood, skin, ulcer, lymph node, gastric washings, or respiratory tract secretions can also yield a diagnosis but the organism is difficult to grow[15]. Polymerase chain reaction testing may provide a rapid and specific confirmation[16]. Histologic examination of the ulcer reveals epidermal and upper dermal necrosis. Chronic lesions demonstrate granulomatous infection with necrotic foci. Lymph nodes show multiple granulomas with central necrosis.

Streptomycin is the preferred treatment. Gentamicin for 7-10 days is an alternative treatment. Treatment failures and high relapse rates have been reported with doxycycline and chloramphenicol[17]. Ciprofloxacin and levofloxacin have been used successfully. Protective clothing and use of chemical repellents when working outdoors in endemic areas should be used. Ticks should be removed promptly. A live attenuated vaccine partially protects against infection resulting from respiratory and cutaneous transmission[18]. A 2 week course of ciprofloxacin or doxycycline is effective in post-exposure prophylaxis when given within 24 hours of airborne exposure.

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