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Q Fever

Clinical Conundrum

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A 75-year-old retired farmer living in rural Saskatche-wan, presented with fever, night sweats, and fatigue for three weeks and a two-day history of bilateral calf pain and lower extremity weakness in August. He report-ed occasional shortness of breath, but denied cough, altered bowel habit, chills, rash, arthralgia, or headache. He had no recent travel history or sick contacts, though he did have contact with animals including sev-eral miniature horses and a pet rabbit on his farm, and frequent attendance at horse shows. In the weeks prior to his presentation he had been working on the farm cleaning out an old barn. There was a positive remote history of multiple tick bites.

Past medical history included hypertension, benign prostatic hypertrophy, rheumatoid arthritis, chronic obstructive pulmonary disease, atrial fibrillation, diver-ticulosis, and granulomatosis with polyangiitis, which had been symptomatic in the past with scleritis and upper airway inflammation but had been quiescent re-cently. Patient was taking methotrexate 10mg/week. At his home hospital the patient's white blood cell count was 17.9×109/L (4.1-10.0) and temperature was 37.2°C, reaching a high of over 38°C. Urine and blood cultures were negative. He was treated empirically with gentamicin 540mg IV q24h and ceftriaxone 2gm q12h.

Despite this antibiotic regimen, the patient's condi-tion did not improve and his temperature continued to spike. After three days in hospital, the patient de-veloped pitting edema to the distal legs bilaterally and weakness to the distal arms and neck. The patient was transferred to our center for further assessment. On evaluation at our hospital, he appeared non-toxic. Vi-tal signs were within normal limits. There was a grade two systolic murmur at the right upper sternal border and marked pitting edema to the legs bilaterally. No lymphadenopathy or rash was present; respiratory and abdominal examinations were unremarkable. Neuro-logic examinations revealed generalized weakness and diffuse hyporeflexia. Laboratory results are outlined in Table 1.

No significant intrathoracic abnormalities were found on chest X-Ray. Computerized tomographic (CT) scan of the chest and abdomen did not reveal any lymphadenopathy or collection of pus. Few indeter-minate pulmonary nodules were seen. Nuclear medicine white blood cell whole body-scan showed no ab-normal uptake and no evidence of occult infection. Nerve conduction studies were normal. MRI of the cervical spine showed degenerative disc changes and bilateral moderate to severe neural foraminal stenosis at C5-6 and C6-7. There was no evidence of discitis or osteomyelitis. Antinuclear antibody test was negative and rheumatoid factor was elevated at 1160 IU/mL. Anti-myeloperoxidase ((MPO) antibody was positive at 47U/ml (0-6). Anti-neutrophil cytoplasmic antibody (ANCA) serology had been negative 3 years ago. He was seen by the rheumatology consult service who, did not think that granulomatosis with polyangiitis was ac-tive. Methotrexate was discontinued.

Q: What is your initial differential diagnosis?

a: Lymphoma
b: Subacute infective endocarditis
c: Tuberculosis
d: Zoonotic infection

Prolonged fever, night sweats, generalized weakness and fatigue are common symptoms of lymphoma, particularly in this age group and was one of the dif-ferential diagnosis in our patient. However, absence of lymphadenopathy, splenomegaly on clinical and radio-logical examination did not show mediastinal or retroperitoneal lymphadenopathy. Bone marrow aspirate revealed a normoblastic erythroid series and myeloid hyperplasia. Megakaryocyte, plasma cell, and lympho-cytic populations were normal. Marrow biopsy showed normocellular normoblastic bone marrow. Myeloid se-ries and megakaryocytes appeared normal, and there was no evidence of granuloma or lymphoma. Reticulin stain showed minimal reticulin fibrosis. These findings make lymphoma very unlikely.

Culture negative infective endocarditis was also on the list of differential diagnoses at this stage. Transesopha-geal echocardiography (TEE) showed bilateral atrial enlargement and aortic sclerosis but failed to reveal any vegetations. Negative blood cultures and absence of vegetation on TEE makes endocarditis less likely.

Although clinical picture of prolonged fevers and night sweats would suggest tuberculosis, absence of cough and negative find-

Table 1. Laboratory results

Investigation (normal range)	Result
White Blood Cell Count, x 109/L (4.1-10.0)	18.3
Neutrophil Count, x 109/L	16.3
Hemoglobin, g/L (120-160)	113
Platelets, x 109/L (150-400)	376
Alkaline Phosphatase, U/L (40-135)	60
Alanine Aminotransferase, U/L (4-55)	86
Aspartate Aminotransferase, U/L (5-35)	82
Bilirubin, µmol/L (2-20)	8
C-Reactive Peptide, mg/L	143.8
Erythrocyte Sedimentation Rate, mm/hr (0-20)	78
Creatine Kinase, U/L (55-170)	117
Anti-Nuclear Antibody (Negative)	Negative
Cerebrospinal Fluid	
Glucose, mmol/L (2.7-4.2)	4
Protein, g/L (0.15-0.60)	0.27
Red Blood Cells Count, x 106/L	191
White Blood Cells Count, x 106/L	1

ings on radiology and bone marrow biopsy make pulmonary or disseminated tuberculosis unlikely. Disseminated tuberculosis however, is often difficult to diagnose, and neither the PPD test nor stains for acid-fast bacilli are sensitive enough to rule out disseminated tuberculosis. Patient had no known exposure to tuberculosis and was not taking tumor ne-crosis factor-alpha (TNF-a) antagonist drugs, which would have predisposed him to tuberculosis.

Gentamicin and ceftriaxone were administered in the peripheral hospital presumably as empiric therapy for an occult infection. Lack of response to broad- spec-trum antibiotic treatment and negative blood cultures should make one aware of the possibility of either a non-infectious cause of fever or an infectious agent that is difficult to culture in the laboratory.

Q: Zoonotic disease was raised as a possibility. Which zoonotic infection is most likely?

a- Histoplasmosis b- Tularemia
c- Brucellosis d- Q fever

The differential diagnosis at this stage was narrowed to: disseminated histoplasmosis, brucellosis, tularemia and Q fever. Histoplasma capsulatum is a thermally di-morphic fungus found in soil, where the organism ex-ists in mycelial phase. Cattle-farming is a risk factor for histoplasmosis. Infection is acquired by inhaling the spores, which are deposited in the lungs. Histo-plasmosis is usually asymptomatic and self-limiting in the normal host. However, progressive disease, either restricted to lungs or disseminated, develops in a small number of patients, particularly in patients with im-munodeficiency [1]. Fever and weight loss are common symptoms. Pulmonary infiltrates are found in about half the patients. Bone marrow involvement can cause cytopenias. Being on immunosuppressant treatment, our patient was susceptible to disseminated histoplas-mosis and could have been exposed to histoplasmo-sis on his farm. However, bone marrow cultures were negative for H. capsulatum and mycobacterial tuberculum. Bone marrow cultures are positive for H. capsulatum in over 90% of patients. Urinary polysaccharide antigen test, which is highly sensitive and specific for H. capsu-latum was negative, thus excluding the diagnosis.

With patient's history of exposure to farm animals and tick bites and sub acute illness with fever, headache, generalized arthralgias, weakness and liver function abnormalities, infection with Francisella tularensis must be considered. F. tularensis can persist for months in mud, water and mammal or bird carcasses and can be spread to humans by ingestion, inhalation, tick and deerfly bites, contact with infected tissues, or an animal bite. Depending on the route of infection, a number of syndromes including ulceroglandular, ocu-loglandular, oropharyngeal, and pneumonic tularemia are recognized [2]. In the 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. Involved lymph nodes may suppurate and drain but there is no associated lymphangitis. Fever, chills, malaise, my-algia, arthralgia, sore throat and fatigue are common symptoms. Oculoglandular tularemia is characterized by painful, purulent unilateral conjunctivitis with cer-vical and periauricular lymphadenopathy. Ingestion of infected food or water may cause oropharyngeal or gastrointestinal tularemia. Oropharyngeal tularemia is characterized by acute exudative pharyngitis, tonsilli-tis or stomatitis with cervical lymphadenopathy. Ton-sils enlarge and 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 dysp-nea. Chest X-ray will show pulmonary infiltrates which may be bilateral and associated with hilar adenopathy. In our patient lack of ocular involvement and pain-ful regional lymphadenopathy makes the oculoglandu-lar and ulceroglandular varieties of tularemia unlikely. Lack of abdominal symptoms, cough, and pulmonary infiltrates on radiological examination make typhoidal

and pneumonic varieties unlikely. Tularemia serology was negative.

Brucellosis can be acquired by drinking unpasteurized dairy products on a farm. Humans acquire brucello-sis from exposure to infected animals or contaminated animal products and would be a consideration in the differential diagnosis of our patients because of his-tory of exposure to farm animals. Although, Canada was declared free of brucellosis in 1985, several isolat-ed cases of bovine brucellosis in livestock were subse-quently identified, with the last known case occurring in a cattle herd in Saskatchewan in 1989 [3]. The incu-bation period for brucella infection is highly variable, ranging from a few days to many months. Brucello-sis, therefore, should be considered a possibility when detailed travel history is not available. Moreover, bru-cellosis may be acquired from ingestion of imported dairy products such as cheese.

Patients with acute brucellosis present with nonspe-cific symptoms, including fever, sweats, malaise, and anorexia. Chronic brucellosis may cause ulcerations of the gastrointestinal tract, splenic abscess or sple-nomegaly, and osteoarticular complications, includ-ing osteomyelitis, arthritis, tenosynovitis, bursitis, and spondylitis. Sacroiliitis is the most frequently reported articular complication of brucellosis . Blood cultures are often negative in brucellosis often yield no organ-isms, and the diagnosis rests principally on serologic test results. Our patient had no recent travel history to brucella endemic areas. Lack of articular symptoms and negative serological tests for brucellosis makes it an unlikely diagnosis in our patient.

Q fever was thought likely at this stage since lympho-ma; infective endocarditis, brucellosis, tularemia, histo-plasmosis and tuberculosis were excluded. Q-fever can cause prolonged fever, abnormal liver enzymes and is associated with exposure to farm animals. Coxiella burnetti serology was positive as outlined in Table 2, confirming a diagnosis of acute Q fever, likely caus-ing granulomatous hepatitis. Q fever can present as an acute or chronic infection.

Q: What is the next step in management?

a- Liver Biopsy
b- Inform Public Health
c- Change treatment to doxycycline and chloroquine

Q-fever causes granulomatous infection of the liver and abnormal liver enzymes are a common finding in Q fever. A diagnosis of granulomatous hepatitis due to acute Q- fever is highly likely in view of abnormal liver enzymes and positive serology for C burnetti, a liver bi-opsy may show characteristic fibrin-ring granulomas. However, liver biopsy is an invasive procedure with risk of complications and will not change management decisions, is not indicated.

Q fever is a reportable disease in Ontario under the Health Protection and Promotion Act and must be reported immediately to the local medical officer of health by telephone. The disease should be reported even if it is only suspected and has not yet been con-firmed[5]. It is not notifiable in Saskatchewan.

Treatment for acute Q fever is doxycycline 100mg twice daily for 2 weeks. Patient's serology and course of illness at this stage suggests acute Q fever. Addi-tion of hydroxychloroquine therefore is not indicated. Treatment for chronic Q- fever is combination of dox-ycycline and chloroquine for at least 1.5 to 3 years. Hydroxychloroquine is added to increase lysosomal pH to enhance activity of Doxycycline in the intracellular compartment where Coxiella resides. Hydroxychloro-quine therefore, should be added to the treatment regi-men if future course of the disease suggests chronicity.

Outcome

Patient was initially treated with doxycycline 100mg twice daily for acute Q fever. Patient complained of recurrent fevers when reviewed 4 weeks later. He also felt generalized weakness and fatigue. Liver enzymes showed a worsening trend. Chronic Q fever was thought likely at this stage. Doxycycline was restarted and chloroquine was added to his treatment. Patient was doing well 4 months after initial presentation. He had no fevers, muscle pains and fatigue had improved significantly and liver enzymes came down to within normal range.

Discussion

Q-fever is a zoonosis caused by Coxiella burnetii, an obligate intracellular pleomorphic gram-negative coc-cobacillus. The reservoir includes a wide variety of animals including cows, goats, sheep, dogs, cats, wild rodents and small mammals, big game wild life, rep-tiles, amphibians, birds, fish and ticks[6]. C burnetii is shed in milk, faeces, urine, and especially in birth by-products. Humans are infected by inhalation of infec-tious aerosol particles from parturient fluids of infect-ed livestock. One does not need direct exposure to the animals since Coxiella burnetii can be carried in dust and wind over large distances. Sporadic cases of human transmission have occurred by consuming unpasteur-ised milk, contact with contaminated clothing, blood transfusion, sexual intercourse, and tick bites. Trans-placental transmission may cause congenital infection.

Q-fever has been reported from most countries ex-cept New Zealand [7]. Incidence varies in different geographic areas, being 500 cases per million people in France, 38 cases per million persons in Australia and 0.28 cases per million persons in USA[8]. The number of cases of Q fever has declined considerably from the 1980s and early 1990s. Q fever was common in Nova Scotia (50-60 cases per year in a population of 950, 000) . Since 2004, only 4-5 cases have been reported each year [10].

Clinical features

Asymptomatic infections are common. After an incu-bation period of 9-28 days, the acute illness presents with an influenza-like illness with headache, fever, my-algia and atypical pneumonia. However, late presenta-tions can occur. Chest radiographs findings are non-specific and pneumonia is mild with non-productive cough with minimal auscultatory findings. Maculopap-ular or purpuric rash occurs in 10% and myocarditis and meningoencephalitis in 1% of cases.

Endocarditis accounts for 60 to 70% of chronic Q fever. Diagnosis is difficult since cultures are usually negative and vegetations absent or small. Most patients with endocarditis have underlying valvulopathies or im-munosuppression. Modified Duke criteria for endocar-ditis takes this into account and serologic evidence of active infection with Coxiella burnetii has been included as a major criterion [11]. After an incubation period of 1 to 20 years

it usually presents with fever, malaise, weight loss, chills, anorexia and night sweats. Other manifestations of chronic Q-fever include osteomyeli-tis, granulomatous hepatitis, infected aortic aneurysms and chronic pulmonary infections. Q fever infection in pregnancy may induce abortion or premature delivery and cause intrauterine growth retardation, intrauterine foetal death, and oligoamnios[12].

Leucocyte count is generally normal but may be ele-vated. Thrombocytopenia is found in 25% of patients. Transaminases are moderately elevated in 85% of pa-tients. Hyperglobulinemia and elevated erythrocyte sedimentation rate are common findings. Rheumatoid factor and autoantibodies including antimitochondrial antibodies, anti-smooth muscle antibodies and antibodies to phospholipids are commonly found in chronic Q fever [13]. Fibrin ring or "doughnut" granu-lomas may be found in liver or bone marrow biopsy specimen.

The diagnosis of Q-fever relies on serological exami-nation. Antigenic phase variation in unique to Coxiella burnetii. Although only phase I organisms are virulent for humans, anti phase II antibodies are the first to ap-pear. Specific high levels of anti-phase I antibodies are normally found in chronic Q fever patients, whereas specific anti-phase II antibodies predominate during acute Q fever. Antibody detection by immunofluores-cence is highly sensitive and specific. A titre of 200 or greater for IgG and 50 or greater for IgM against phase-II antibodies indicates acute Q-fever with 100% specificity. IgG titre of 800 or greater against phase-I antibodies is diagnostic of chronic infection. Phase-II antibodies peak by 2 months but can be detected with-in 2 weeks of infection in most patients. Phase-I IgG antibody titre of ≥800 has a sensitivity of 100%, speci-ficity of 99.6%, positive predictive value of 98.1% and negative predictive value of 100% [14]. This value has been proposed as a major criterion in modified Duke criteria to facilitate diagnosis of Q-fever. A serum sam-ple with a phase I IgG titer of ≤800 is highly predic-tive of chronic Q fever (98%) and is 100% sensitive. Moreover, a serum sample with a phase I IgG titer of ≤1,600 is 100% diagnostic of chronic Q fever. Culture of organism is difficult and highly infective, requiring biosafety level-3 containment. It is also a potential weapon of bioterrorism.

Treatment

Our patient was discharged on doxycycline 100 mg twice daily and hydoxychloroquine 200mg three times daily with follow-up arranges as out patient. The treat-ment of choice for acute Q-fever is oral doxycycline 100mg every 12 hours for 12 to 14 days. Cotrimoxazole is recommended for pregnant women and young chil-dren. Pregnant patient treated with cotrimoxazole may require treatment with doxycycline and hydroxychloro-quine for chronic Q-fever post-partum. Two different treatment protocols have been evaluated: doxycycline in combination with quinolones for at least 4 years and doxycycline in combination with hydroxychloroquine for 1.5 to 3 years. The second therapy leads to fewer relapses, but requires routine eye exams to detect ac-cumulation of chloroquine. The efficacy of doxycy-cline/hydroxychloroquine combination treatment has been confirmed in a study comparing with the stand-ard treatment of doxycycline (100mg) twice daily and ofloxacin (200mg) 3 times daily16. This treatment should be continued for 18 months to 3 years. How-ever, the optimum duration of treatment is unknown.

The ratio of serum doxycycline concentration to MIC should be monitored during the course of therapy in patients with Q-fever endocarditis and should be maintained ≥1 since patients with a ratio between 0.5 and 1 show a low decline of antibody levels compared to those with a ratio of ≥117. In practice, however, ob-taining MIC values and doxycycline levels are difficult and not available in most laboratories.

IgM and IgG antibody titres to phase-I should be monitored every 3 months during therapy until they are less than 1:200. IgM antibodies disappear first, fol-lowed by IgA antibodies. IgG titres may remain posi tive for years. Relapse rate is high even with combina-tion therapy and antibody titres should be monitored once the treatment is discontinued. A 4-fold rise indi-cates relapse. Follow up for life may be needed.

Farmers, ranchers and farm workers in contact with cattle, sheep and goats; meat packers, rendering plant workers, hide and wool handlers; hunters and trappers; laboratory animal researchers and support staff; and workers who care for pets and livestock, veterinary personnel, pet-shop workers and zoo attendants are occupations at risk of Q fever and should take precau-tions when handling animals or animal products. The risk can be reduced in high- risk workers by vaccina-tion of workers, personal precautions, and workplace hygiene. The use of this vaccine should be limited to those at high risk of exposure whose blood tests for resistance to Q fever are negative. Before vaccination, workers must also have a skin test to determine if they are allergic to the vaccine [15].

Conclusion

Q-fever should be sought as a diagnostic possibility when a patient presents with fever of unknown origin, has a relevant history of exposure to animals and when the blood cultures and other radiological conditions do not find an alternative cause of patient's symptoms.

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