

Case Report

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Diagnosis Based on History, Not Examination

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ABSTRACT

Cat scratch disease (CSD), caused by the bacterium *Bartonella henselae*, is usually self-limiting, presenting with low-grade fever and tender lymphadenopathy. With delayed diagnosis or reactivation of latent disease, CSD is associated with severe debilitating symptoms. We are presenting a patient who proved a diagnostic challenge, before being found to have reactivation of *Bartonella henselae*, requiring three-months IV Trimethoprim-Sulfamethoxazole and Hydrocortisone.

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Case Presentation

We are presenting a patient with prolonged fever, skin rash and epitrochlear lymphadenopathy who presented a diagnostic challenge for two-weeks before being diagnosed with cat scratch disease (CSD).

A 55-year-old female, presented to her GP feeling generally unwell with skin rash on her right chin. Past medical history was significant for type 2 diabetes, managed with slow release Metformin. Her HbA_{1c} was 7 and she had regular GP follow-up and no diabetic complications. She was a non-smoker and non-drinker and lived with her partner for the last 30 years in Port Headland, Western Australia. The patient was a breeder of five cats and two kittens, all of which were healthy. The patient was of Asian descent, with a family history of extrapulmonary tuberculosis and no history of chronic disease. She last visited the Philippines two-years prior to presentation.

Examination by GP revealed temperature of 38.0, HR 70/min regular and BP 125/70. There were no meningeal signs, cardiac and chest examination were unremarkable, abdomen was soft, non-tender with a palpable spleen. There was a non-tender rash on the right chin. The rest of the examination was unremarkable. The patient was prescribed Augmentin and Clavulanic Acid for one week, with no response. She presented to her GP the following week with a fever and the development of loss of weight and anorexia. Clinical examination remained unchanged. Augmentin was continued with the addition of Doxycycline; however the

Doxycycline was self-ceased by the patient due to intolerance with development of dyspepsia and a metallic taste.

On second presentation, the GP ordered basic bloods, including full blood count (FBC), urea, electrolytes and creatinine (UEC), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), blood and urine culture, all of which were normal. A chest x-ray was performed with no signs of cardiomegaly or parenchymal lung disease. Five days later the patient presented to the GP for the third time, with ongoing fever and was transferred to the hospital for further investigations and management. The patient was seen by a medical registrar and the examination findings were consistent with the GP: a skin rash on the right chin, low grade fever, no haemodynamic instability with the rest of the examination unremarkable.

A septic screen was performed, including throat swab, skin swab and echocardiogram. IV fluids and Paracetamol were commenced. The only positive findings were a CRP 100mg/L (reference 0-10mg/L) and ESR 80mm/hr (reference <20mm/hr). Skin swab had no growth and echocardiogram did not show vegetations. The patient was examined by an infectious disease consultant. Findings included temperature 38.0, HR 70/min regular and BP 130/80, no neck stiffness, normal appearance of the retina on fundoscopy, normal cardiac and chest examinations. There were no axillary lymph nodes and few tender, non-matted submental and epitrochlear lymphadenopathy, ranging in size of 5-10mm. Liver and spleen were palpable, with mild tenderness on the epigastrium and no fluid in the abdomen. The non-tender rash on the right chin was diagnosed as granuloma annulare, a skin manifestation of diabetes mellitus.

Differential diagnosis by infectious disease doctors included lymphoma, autoimmune disease –namely systemic lupus erythematosus, severe viral illness, mononucleosis or toxoplasmosis. They hypothesised it was unlikely to be a solid neoplasm or leukaemia. Basic bloods were repeated, as well as a blood culture, autoimmune screen, viral studies and a punch biopsy. Autoimmune screen included Rheumatoid Factor, Anti-Nuclear Antibodies, Extractable Nuclear Antigen Antibodies, Anti-Cyclic Citrullinated Peptides, Anti-Centromere Antibodies, Vasculitis Screen, Flow Cytometry, Immunophenotyping, protein and urine Electrophoresis, Light Chain Assay, Procalcitonin and Serum Calcium. Viral studies included PCR for Cytomegalovirus, Epstein-Barr Virus, serology for Toxoplasmosis, Dengue Fever and Q-fever. Findings were either negative or normal. Whole body computerised tomography (CT) scan was completed and revealed mesenteric lymphadenopathy.

The patient complained of increasing fatigue, with worsening anorexia and an ongoing fever. Infectious disease treated her for extrapulmonary Tuberculosis, in the context of the family history and the patient's ethnicity. A biopsy from the epitrochlear lymph node and sputum sample were sent for PCR for acid-fast bacilli staining. The patient was started on Isoniazid, Pyridoxine, Rifampicin, Pyrazinamide and Ethambutol. Epitrochlear and mesenteric lymph node biopsies were sent for culture in addition to molecular biology with PCR, for broad-range 16S ribosomal RNA and specific gene sequencing. The biopsy was also stained with acid-fast bacilli for isolation of mycobacteria, Grocott-Gomori's methenamine silver staining for isolation of fungi, immunohistochemistry for isolation of Toxoplasmosis, Cytomegalovirus, Treponema Pallidum and serology for Bartonella and Brucella species.

The patient could not tolerate Isoniazid and developed high liver transaminases, it was subsequently ceased and, upon advice from bacteriology, replaced with Moxifloxacin. There was no improvement, therefore Hydrocortisone was commenced. Skin and lymph node biopsies showed stellate abscesses with an abundance of lymphocytes. Warthin-silver staining showed an abundance of small curved Gram-negative bacilli surrounding the blood vessel walls, consistent with a Bartonella infection. Serology for *Bartonella henselae* (*B.henselae*) showed an IgG titer of 1:1246 (reference <1:128) and IgM 1:1480 (reference <1:20). *Bartonella quintana* showed an IgG titer of 1.1812 (reference <1:128). PCR confirmed the *Bartonella* infection and titers were consistent with a reactivation of a latent *Bartonella* infection.

Given the severity of the infection, Hydrocortisone was continued to prevent Jarisch-Herxheimer reaction, and intravenous Trimethoprim-Sulfamethoxazole for three months. The patient continued to improve, with resolution of all symptoms and repeat serology at 6-weeks showed significant improvement in IgG and IgM titers.

Discussion

CSD is a benign disease that usually presents with a low-grade fever with tender regional lymphadenopathy. CSD has a worldwide distribution, although it is most commonly seen in temperate climates where pets are kept indoors [1].

CSD is transmitted by cats infected with the Gram-negative intracellular bacterium *B.henselae*. Cats are a natural reservoir for *B.henselae* which is commonly isolated in feline erythrocytes of asymptomatic cats [2]. The bacterium spreads between cats through the arthropod vector fleas, and is known to contaminate

feline saliva [2]. *B.henselae* is transmitted to humans through cat exposure, usually through a cat-scratch or bite. It should be noted however, that this is not the only route of transmission, studies have shown that *B.henselae* can also be transmitted through the faecal-oral route, with the bacterium viable in flea faeces for more than 7 days, another case study found *B.henselae* was transmitted through the bite of a red ant [3,4].

In most patients CSD is self-limiting and does not require treatment, however occasionally it can be manifested by severe symptoms. This was seen in our patient who presented with a prolonged fever, loss of weight, anorexia, hepatosplenomegaly and mesenteric lymphadenopathy. In patients with suspected CSD and abdominal pain there should be a low threshold to perform contrast CT, to aid the diagnosis of mesenteric lymphadenopathy and guide treatment appropriately. Other serious complications include Meningoencephalitis, Hepatitis, Retinitis, Choroiditis, Arthritis, Adenopathy, Hepatic Peliosis and Osteomyelitis. In immunocompromised patients, including those with AIDS, there is concern for the development of Bacillary Angiomatosis and Bacillary Peliosis [2].

Another common presentation of CSD is fever of unknown origin. A study of 130 seropositive patients with CSD found 37% of patients presented with fever of unknown origin and almost half lacked lymphadenopathy [5]. Another study of patients with CSD presenting with fever of unknown origin found 32% of patients underwent unnecessary invasive diagnostic procedures and 21% were initially diagnosed with lymphoma [6]. It is in these patients that the importance of a thorough clinical history is paramount. A lack of clinical suspicion was a contributing factor in the delay of diagnosis for our patient and with early diagnosis and treatment the natural progression of disease may have been altered with a reduction in the required treatment period. As mentioned above, although the majority of cases involve a cat-scratch or bite, a lack of the same should not exclude CSD as a differential diagnosis. This is for two reasons, one of which is the fact that a patient may not be aware of the trauma from an infected and asymptomatic cat, but also that CSD can be transmitted through the faecal-oral route [3].

A concerning feature of CSD is the potential for the development of more severe symptoms in patients that have reactivation or reinfection of *B.henselae*, characterised by an IgG titer >1:128. With an IgG of 1:1246, our patient had a reactivation of *B.henselae*. A study looking at 48 patients with *Bartonella* endocarditis found that the patients with raised IgG titres had a delayed recovery and required an extended period of treatment [7]. Extended periods of time in which the bacteria remains in the blood stream is associated with prolonged antigenic stimulation, in turn leading to reduced response to treatment, prolonged disease and the requirement for extended treatment with antibiotics [7].

Additionally, a case study of a patient with AIDS, presenting with a year long history of tender lymphadenopathy was investigated comparably to our patient. On presentation, the patient complained of tender lymphadenopathy and fever. Initial investigations were negative, including a lymph node biopsy for Tuberculosis, fungal infection and lymphoproliferative disorders (8). It wasn't until the following year that CSD was considered as a differential diagnosis and confirmed through Warthin-silver staining. Similarly to our patient, once given the appropriate diagnosis the patient required an extensive period of treatment and responded well to a 12-week course of Azithromycin [8].

This case highlights the importance of increased awareness of CSD to aid in early clinical diagnosis and appropriate treatment. Thorough clinical history is crucial in aiding the diagnosis of CSD, particularly in patients presenting with fever of unknown origin and those with delayed diagnosis, however CSD should not be excluded in patients without known physical contact with cats.

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