CASE REPORT

The cat did it: erythema nodosum and additional atypical presentations of *Bartonella henselae* infection in immunocompetent hosts

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SUMMARY

A healthy patient presented with painful skin lesions on the anterior surface of her legs. Erythema nodosum was diagnosed but all the usual causes were ruled out. The finding of bilateral enlarged axillary lymph nodes with necrosis and granulomas led to the diagnosis of *Bartonella* infection, an unusual cause of erythema nodosum. Imaging also revealed splenomegaly and small para-aortic lymph nodes. Up to one quarter of the patients with cat-scratch disease present atypically, a considerably higher prevalence than previously reported. A comprehensive review of the literature (PubMed, since inception, all languages) revealed a remarkable array of unusual presentations which are summarised and briefly discussed.

BACKGROUND

Since pleomorphic organisms were first identified in 1983 by the Armed Forces Institute of Pathology in the lymph nodes of most of the patients with cat-scratch disease (CSD), major advances in the diagnosis have been achieved. The *Bartonellas* are now recognised as emergent infectious agents, and the spectrum of possible manifestations of disease is still expanding.¹ The remarkable heterogeneity of the clinical presentations of CSD in immunocompetent patients may lead to poor recognition and delays in diagnosis and treatment. The difficulty is increased by the fact that a substantial minority of patients fail to report a scratch and in some cases, even deny contact with cats.¹ We report an unusual cutaneous presentation of *Bartonella henselae* infection in an immunocompetent adult and present a review of the literature to draw attention to the myriad different atypical presentations reported for cat-scratch disease, differentiating between the unusual and the rare.

CASE PRESENTATION

A healthy 53-year-old woman was referred with a couple of weeks history of erythematous nodules on her legs. The nodules were several centimetres large, tender to painful and appeared asymmetrically over the anterior aspect of both shins and thighs, associated with bilateral +2 pitting oedema. Over time, older nodules showed spontaneous receding and new lesions developed. She denied fever or sweats, took no drugs and had no change in bowel habits or chest symptoms. Family history was non-contributory.

On admission, she had tender right axillary lymphadenopathy but no other notable findings on examination. Chest X-ray and ECG were normal. Haemoglobin was 11.0 g/dL, white blood cells $6.4 \times 10^9/L$, platelets $215 \times 10^9/L$, erythrocyte sedimentation rate 26 mm/hour, C-reactive protein 26 mg/dL, serum albumin 40 g/L, globulins 30 g/L with normal urinalysis, renal function, electrolytes, lactate dehydrogenase and liver enzymes.

INVESTIGATIONS

Diagnosed as erythema nodosum, a diagnostic workup for its underlying cause included ruling out streptococcal infection (negative throat swab culture and antistreptolysin O antibody); viral serology (IgM negative for herpes viruses and hepatitis A virus, negative for hepatitis B and C viruses and for HIV); Brucellosis and toxoplasmosis (negative), tuberculin test and serum ACE (both normal); fundoscopic examination (normal); gynaecological examination (normal), abdominal ultrasound and echocardiography (both normal). Abdominal CT with oral and intravenous contrast showed splenomegaly (14.5 cm) and small para-aortic lymph nodes. Multiple scattered hypodense lesions in the liver were suspected to be partly due to cysts. Chest CT revealed extensive bilateral axillary lymphadenopathy with associated lymph node necrosis and without lung or mediastinal pathology (figure 1). Mammography and tumour markers were normal.

Learning that she had been regularly feeding cats in her backyard, *B. henselae* infection was sought, although there was no history of a scratch. Serology was strongly positive for IgG (titre $\geq 1:512$) and IgM positivity was detected in indirect immunofluorescence assay. A CT-guided needle biopsy of axillary lymph node demonstrated necrotising granulomas with negative Periodic acid-Schiff stain (PAS), silver and Ziehl-Neelsen stains and negative PCR for acid-fast bacilli. A PCR for *B. henselae* required an outside laboratory and was not authorised due to cost, the availability of other data strongly supporting the diagnosis, complete response to treatment and absent alternative explanation.

DIFFERENTIAL DIAGNOSIS

Erythema nodosum can be seen as a sign of systemic disease. Its wide differential includes association with 'usual' bacterial infections (in particular, streptococcal sore throat but also infections with *Yersinia*

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Figure 1 Axial (A) and (B) and coronal (C) contrast-enhanced CT images of the chest showing bilateral axillary lymphadenopathy. Enlarged necrotic lymph node (arrow in A and C) and solid enlarged lymph node (dashed arrow in A) are seen in the right axilla. Note the enlargement of the spleen, measuring 14.5 cm in the craniocaudal view (C).

spp, mycoplasma, chlamydia, campylobacter, rickettsiae, etc); granulomatous diseases (sarcoidosis, tuberculosis (TB), brucellosis, *Bartonella*, histoplasmosis); viral infections (in particular, herpesviruses, hepatitis B and C viruses, HIV); varied drugs (such as antibiotics, oral contraceptives); pregnancy; inflammatory bowel disease and malignancy, mostly haematological. More than half of the cases remain idiopathic.

The differential of multiple hypoattenuating liver lesions is large and includes cysts, haemangiomas, metastatic malignancy and microabscesses. In our patient, some lesions were previously noted and their appearance was consistent with simple cysts. Others probably represent hepatic granulomas characterised by a nodular aggregate of epithelial cells and macrophages, surrounded by lymphocytes as seen in hepatosplenic *Bartonella* infection. However, a biopsy to prove it was not considered prudent.

Areas of necrosis within enlarged lymph nodes as demonstrated by our patient's chest CT (figure 1) and confirmed by her lymph node biopsy is quite a distinctive finding, suggestive of either malignancy (such as metastatic squamous cell carcinoma, Hodgkin's or non-Hodgkin's lymphoma, etc), granulomatous disease (especially TB, also sarcoidosis, cat-scratch disease, tularemia), herpes simplex lymphadenitis and Kikuchi disease. (Kikuchi disease, or histiocytic necrotising lymphadenitis, is a benign, self-limited disease, predominantly involving cervical lymph nodes that show necrosis with dominance of histiocytes in its later stage). The imaging appearance is usually non-specific and requires confirmation, such as by biopsy of the lymph node.

However, to be included in the differential diagnosis in our patient, an entity that fulfils all above-mentioned features must be selected so that the short list includes only TB, sarcoidosis, herpes simplex virus infection, cat-scratch disease and lymphoma.

TREATMENT

She was treated with azithromycin² at a dose of 500 mg on day 1 and 250 mg/day for 4 days and discharged home on the fourth hospital day.

OUTCOME AND FOLLOW-UP

Recovery was slow, over 4 weeks, however, on follow-up in the hospital clinic at 2 months she was asymptomatic with normal

physical examination and normal laboratory tests. The patient remained in the care of her primary physician who was contacted and confirmed well-being 8 months after discharge.

DISCUSSION

Serology alone is insufficient for the diagnosis of *Bartonella* infection since low-titre IgG antibodies can be found in up to 9% of healthy asymptomatic adults, especially those with cat exposure.^{3,4} However, the presence of IgM antibodies and high-titre IgG against *B. henselae*, the bilateral axillary lymphadenopathy with necrosis and granulomas by imaging (figure 1) and biopsy, the absence of any other identifiable cause and favourable outcome strongly support the diagnosis in a patient with daily contact with cats.¹⁴ In addition to the erythema nodosum, the patient's splenomegaly, para-aortic lymph node enlargement and possibly the hypodense liver lesions, although not biopsied, likely represent visceral involvement,⁵ typically associated with minimal laboratory tests abnormalities.

Erythema nodosum constituted the presenting manifestation of *B. henselae* in our patient. This is an unusual manifestation of CSD, reported in very few patients as the presenting symptom and sign.^{6,7} Erythema nodosum is the most common form of panniculitis—inflammation of the subcutaneous fat tissue, and can be associated with myriad precipitating factors. Among four relatively recent (1998–2007), well-documented series from Europe comprising 467 patients with erythema nodosum, no identifiable cause could be found in up to 55% of the patients (range, 34%–55%).^{8–11} Infections were the leading identifiable underlying aetiology, primarily streptococcal infections (~25%, range 11%–28%). Also, 12%–29.5% had sarcoidosis or (less often) TB (median 23% for both granulomatous diseases). Other notable causes included Behcet's disease, inflammatory bowel disease and pregnancy. Malignancy was rare (1% in one series).⁹ None of those 467 patients had evidence of *Bartonella* infection.

CSD is a zoonosis caused mainly by *B. henselae*—a highly prevalent infection of cats.¹² Typical presenting symptoms of CSD include a non-tender papule in the scratch line (inoculation site), regional lymphadenopathy most commonly involving the cervical and axillary lymph nodes and non-specific systemic symptoms such as fever, headache and malaise.¹³ However, in contrast with earlier series that reported a low prevalence of atypical manifestations of about 5%,¹³ it is now recognised that a sizeable proportion of patients develop atypical manifestations, and these may occur on the patient's presentation, show remarkable heterogeneity (box 1) and pose considerable diagnostic difficulty, more so, since the zoonotic link may not be obvious. In one study, 34% of patients with CSD had no history of cat-related trauma and approximately 17% had 'negligible' contact with cats.¹²

For example, 21% of 130 seropositive patients with CSD presented atypically,¹⁴ and in another series, 24% had atypical manifestations.¹² When CSD patterns were compared between patients aged <60 years and >60 years, the likelihood of atypical manifestations was significantly increased in the elderly group (33 vs 14%).¹⁵ Among them, the most notable were fever of unknown origin, infective endocarditis, visceral (hepatosplenic) involvement, encephalopathy, posterior ocular segment involvement, arthropathy and skin manifestations. Of 841 CSD patients, 21 had erythema nodosum (2.5%),¹⁶ and in the largest series of 1200 patients seen at a single private practice, just five patients had erythema nodosum (0.4%).¹³ In smaller series, erythema nodosum was not represented.^{12,14}

Box 1 Unusual ('atypical') manifestations of *Bartonella henselae* infection in immunocompetent patients*

Systemic

- Fever of unknown origin (~7%–8%)^{14 15} May occur without lymphadenopathy;
- Infective endocarditis (IE,) (~10% of culture-negative IE)^{1 17 18} — including embolic stroke, associated glomerulonephritis, etc. May occur without lymphadenopathy;
- Hypercalcaemia† — calcitriol overproduction by the granulomas.¹⁹

Abdominal ('visceral')

- (~1%)^{5 12 14} including upper abdominal pain, hepatosplenomegaly (liver enzymes characteristically normal, the diagnosis is ultrasound-based) due to reticuloendothelial system granulomas. May occur without lymphadenopathy;
- Granulomatous hepatitis;
- Hepatosplenic microabscesses/abscesses;
- Solitary splenic abscess†.²⁰

Neurological

- Encephalitis/encephalopathy (~3%)^{14 21 22} — including headache, mental status changes, expressive aphasia, seizures (typically normal imaging, minimally abnormal cerebrospinal fluid, non-specific EEG), mostly due to cerebral vasculitis;
- Transverse myelitis†^{23 24};
- Cranial nerve palsy (VI, VII)†;
- Paraesthesia, peripheral neuritis, Guillain-Barre syndrome†;
- Cerebellar ataxia†.

Dermatological

- Maculopapular rash (~6%–7%)¹²;
- Erythema nodosum (~2%–2.5%)¹⁶;
- Cutaneous vasculitis†;
- Urticaria†;
- Papuloedematous eruption†;
- Immune thrombocytopenic purpura†;

Ocular

- Neuroretinitis (up to 4.6%)^{25 26} — including acute decrease in visual acuity and often an afferent papillary defect;
- Granulomatous conjunctivitis (~8%)²⁷ (with associated preauricular/submandibular lymphadenopathy, termed Parinaud oculoglandular syndrome);
- Optic neuritis†.

Musculoskeletal

- Arthropathy (~5%–6%), arthralgia and/or arthritis (ratio 3:1) involving medium–large joints, often with morning stiffness¹⁶ m
- Myalgia/proximal myositis (~6%)²⁵;
- Tendinitis†;
- Back pain†;
- Vertebral osteomyelitis/osteolytic lesion†.

Ear, nose, throat

- Parotid involvement (~6%)²⁶ — including intraglandular lymphadenopathy;
- Acute mastoiditis†;
- Deep neck space infection†.

Continued

Box 1 Continued

Thoracic†²⁷

- Pulmonary infiltrate—pneumonia;
- Pleural effusion;
- Mediastinal mass;
- Myopericarditis.

Vari†

- Sterile abscess in unusual locations (eg, chest wall, orbit, etc); odynophagia; exacerbation of IgA nephropathy; mass protruding through the duodenal wall.

*Reported in up to 24% of the patients (A, B) and may often be the presenting features of cat-scratch disease. Based on extensive search of the literature (PubMed, bartonella AND manifestations OR presentation; all languages, since inception; plus references list of relevant studies). Full references for the table are available from the corresponding author on request. In about 40% of these patients, lymphadenopathy was not found,¹⁴ adding to the difficulty in diagnosis.

†Extremely rare.

Thus, although erythema nodosum is the third most common dermatological manifestation of CSD (following papule at the inoculation site and a maculopapular rash), it still constitutes a very uncommon presentation which is not widely known. Clinicians should be aware of the highly heterogeneous manifestations of CSD (box 1), including its possible presentation with EN.

Learning points

- Erythema nodosum is a rare presenting symptom of *Bartonella* infection.
- Visceral (hepatosplenic) cat-scratch disease can occur without organ enlargement and without liver enzyme disturbances.
- A substantial number (up to 24%) of patients with cat-scratch disease may present atypically, with either fever of unknown origin, infective endocarditis, hypercalcaemia, hepatosplenic involvement, encephalopathy/encephalitis, neuroretinitis, myalgia, arthropathy, rash or erythema nodosum and varied other rare manifestations. These patients may or may not have an associated lymphadenopathy.
- A high index of suspicion is warranted in view of these highly heterogeneous manifestations, especially in elderly patients, as a substantial minority of patients have no history of a scratch and a few even deny animal contact.
- Diagnosis is based on compatible findings (often, with associated lymphadenopathy and necrotic area); high-titre IgG and IgM antibodies; PCR positive for *Bartonella* in infected tissue and ruling out alternative diagnoses.

Contributors All authors treated the patient and participated in preparing the manuscript, primarily written by AS. AS and ID planned the study and reported the patient. AS conducted the review of the literature and is responsible for box. LU undertook the analysis of the imaging studies and performed the biopsy.

Competing interests None declared.

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