Bartonellosis: light and shadows in diagnostic and therapeutic issues

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ABSTRACT

Cat-scratch disease involves a prolonged and/or complicated course, and lymph node drainage is usually required. Culture and molecular techniques often yield negative results, but immunofluorescence assays may give early information, and elevated antibodies may persist for months. Cat-scratch disease should be suspected in patients with prominent swelling of lymph nodes draining from the upper limbs, limited systemic involvement, and typical epidemiological–clinical features. The temporal antibody response during the sub-acute course remains unknown. Although biomolecular assays are available, the time between onset and investigation is an obstacle to positive results. The role of surgical debridement and the unpredictable activity of antimicrobial agents warrant further investigation.

Keywords Bartonella henselae, bartonellosis, cat-scratch disease


The spectrum of disease caused by Bartonella spp. has expanded rapidly over the past two decades, prompted by the association of cat-scratch disease (CSD), AIDS-related bacillary angiomatosis and bacillary peliosis with the fastidious Gram-negative bacillus identified initially as Rochalimaea henselae, but placed subsequently, on the basis of genomic sequence analysis, in the genus Bartonella [1,2]. Five major Bartonella spp. have been found to be pathogenic (B. bacilliformis, B. henselae, B. quintana, B. elizabethae and B. claridgeiae), but other members of the genus have been found in animal reservoirs (rodents and moles) [1–4]. About 40% of domestic cats may have asymptomatic B. henselae infection accompanied by bacteraemia, which may persist for >1 year and represents the most obvious risk for CSD.

The usual presentation of B. henselae infection is CSD, a sub-acute, regional lymphadenitis usually persisting for 3 weeks or more. This disease, first thought to be caused by Afipia felis, has been attributed to B. henselae since 1992, following isolation of B. henselae from healthy cats and the development of reliable diagnostic tests [1,3–5]. Another species, B. claridgeiae, has been associated rarely with cases of CSD [1,2]. B. henselae antibody is found in 84–100% of CSD patients, and culture from lymph nodes and detection of specific genomic sequences of B. henselae have been achieved [3,4].

Epidemiologically, 87–99% of patients with CSD report contact with cats (whose infection is transmitted by the cat flea Ctenocephalides felis). The exact mechanism of cat-to-human transmission remains unclear, although a scratch or bite is documented in c. 50% of episodes. Cases often involve children or adolescents, but can occur at any age [2,5]. In a study of 130 seropositive patients, it was found that 79.2% of cases occurred at an age of <18 years [2,6,7]. Extensive studies of B. henselae seroprevalence are lacking, but infections rarely occur in the absence of suggestive signs and symptoms [8].

The CSD incubation period is estimated to be 7–15 days. A few non-pruritic papules or papulovesicles (often overlooked) may follow the inoculation lesion, and these precede the characteristic regional lymph node involvement. The first and second set of lymph nodes draining the infection site are usually affected (cervical, axillary or epitrochlear), but more distant sites may be involved infrequently [1–7]. The duration of lymph node enlargement is usually limited to 1–2 months, but may be >1 year [1–5], despite
surgery and antimicrobial therapy. The ‘Parinaud ocu- lograduinary syndrome’ is characterised by a conjunctival site of entry, followed by pre-auricular lymphadenopathy [2,6,9].

Although CSD is usually self-limiting within a few weeks or months, a locally severe disorder or disseminated illness may occur. Granulomatous disease of the liver, spleen, mesenteric lymph nodes, heart and bone, with general or focal signs and symptoms, has been reported [1–5,10,11]. Encephalopathy occurs 2–3 weeks after the onset of disease as a complication in 5% of patients, with sudden seizures, altered behaviour or consciousness, peripheral facial nerve paresis and myeloradiculitis, but self-resolution is the rule [1–3,5]. Haematological manifestations include haemolytic anaemia, thrombocytopenia and eosinophilia, while rare cases of leukocytoclastic vasculitis, mediastinal masses, atypical pneumonia and pleural effusion, and other presentations mimicking collagen vascular diseases, may occur [1–5,10]. The differential diagnosis of CSD includes virtually all possible causes of lymphadenopathy, e.g., pyogenic and Toxoplasma gondii lymphadenitis, atypical mycobacterial infection, haematological and solid-organ malignancies, tularaemia, and brucellosis [1–5]. Of 454 patients with unclear head–neck masses, 61 (13.4%) were confirmed as having CSD [11]. In another series, prolonged fever of unknown origin was the predominant symptom in 2.8% of 130 cases, while 30% of patients with documented serological B. henselae infection lacked any lymphadenopathy [6]. Immune effector cells producing angiogenic cytokines following stimulation with B. henselae may have a role in pathogenesis for immunocompromised hosts developing bacillary angiomatosis and peliosis, while the typical slowly progressing granulomatous response of healthy patients might be triggered by an enhanced immune response to bacterial antigens [3,4,12].

CSD may be suspected on epidemiological–clinical grounds, but serological assays that show a good correlation between infection and disease are available, including indirect immunofluorescence, haemagglutination and enzyme-linked assays. However, comparative studies are lacking, the timing of the IgG and IgM response remains variable, and cross-reactivity between different Bartonella spp. may occur [1–3,8,13,14]. In a long-term parallel serological–clinical follow-up of 98 CSD patients by ELISA for a median of 35.3 weeks [14], anti-B. henselae IgM was detected in 53% of subjects for 3 months, while 25% of patients remained IgG-seropositive for >12 months. Unfortunately, no association was found between the kinetics of the antibody response, the evolution of clinical symptoms (typical or atypical), and the overall duration of illness or time to complete cure [14]. Use of a coupled immunofluorescence test with both serum and lymph node smears has improved the sensitivity and specificity of CSD diagnosis significantly (up to 97.4% based on at least one positive test), and this approach can be used when molecular tests are unavailable [15].

Although serology is the cornerstone of the aetiological diagnosis of CSD, different techniques vary in sensitivity according to the antigen, cut-off levels and other procedures used, so that results from different series are not comparable [8,13,14]. Culture, PCR and other molecular tests are usually confined to reference centres [3,11,13]. Recovery from blood requires prolonged incubation in highly enriched media or endothelial cell lines, while B. henselae DNA can be detected only in the first 6 weeks of the disease. Consequently, molecular assays are often frustrating, since most patients are only investigated several weeks following the onset of disease, and the incubation period is often overlooked. Other routine tests are unhelpful, although hepatic transaminases may be elevated, and ultrasonography and/or computed tomography examinations may show enlarged lymph nodes and disclose the infrequent granulomatous involvement of visceral organs [1,2]. Diagnostic imaging may also help in the differential diagnosis of the most common localisation of lymphadenopathy (the epitrochlear region), and it has been reported that lymphadenopathy at this site is caused predominantly by B. henselae infection [16].

The need for, selection and duration of antimicrobial therapy for CSD remain contentious. Some authors claim that there is no benefit, compared to conservative symptomatic care and follow-up, for immunocompetent, otherwise healthy paediatric or adult patients, while others attribute a significant role to a broad spectrum of antibiotics [1–5,17]. Most isolates of Bartonella spp. appear to be susceptible in vitro to a wide range of β-lactams, rifampicin, erythromycin and tetracyclines, while sensitivity to clindamycin,
quinolones and co-trimoxazole seems to be variable [1–4,18]. However, a remarkable discordance between the in-vitro and in-vivo activity of several antibiotics has been demonstrated. Controlled clinical data are scarce, but in most studies a poor response to penicillin derivatives and other compounds has been found, despite apparent susceptibility in vitro [5,18]. A single placebo-controlled trial with azithromycin showed some initial benefit, but contrasting long-term results [17]. Therefore, the role and mode of antimicrobial therapy for CSD deserve investigation. If treatment seems indicated clinically, novel macrolides, co-trimoxazole, rifampicin, fluoroquinolones and gentamicin might be first-choice agents [2,17,18]. Corticosteroids as adjunctive therapy have been suggested for long-lasting CSD [19] if an exaggerated immune response is present [4,5,13], but no controlled data are available. Suppurative nodes that become tense and painful should be drained, but incision of non-suppurative lesions should be avoided, as chronic draining fistulae or compromised healing may result [1,2,5,7].

Transmission of CSD between humans has not been documented. However, infrequent concomitant disease may occur in siblings [20]. Preventive measures involve avoidance of close contact with cats and cat fleas, and an improved awareness of the risk from cat (especially kitten) scratches.

REFERENCES