Review

Skin manifestations of Bartonella infections

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Introduction

The recognition of the bacteria family *Bartonellaceae*, genus *Bartonella* has expanded during the past decade from the single *Bartonella bacilliformis* to 17 currently identified species (Table 1). At least six of these (*B. bacilliformis, B. henselae, B. quintana, B. elizabethae*, *B. clarridgeiae and B. vinsonni arupensis*) are responsible for human diseases.[1,2] The growing knowledge in this field of pathology and the new insights provided by molecular biology suggest that the number of recognized *Bartonella spp*. and human diseases caused by them will continue to increase in the coming years.

This review focuses on the cutaneous manifestations of bartonelloses, emphasizing selected controversial topics about angiomatous skin lesions.

Table 1 Bartonella spp. pathogens in humans and animals. Adapted from [1,2]

Species	Year of original description	Hosts	Arthropod vector
B. bacilliformis	1907	Human	Sandfly
B. talpae	1911	Mole	
B. quintana	1917	Human	Body louse
B. peromysci	1942	Deer, mouse	
B. vinsonni vinsonni	1946	Vole	
B. henselae	1992	Cat, Human	Cat flea
B. elizabethae	1993	Rat, Human	
B. grahamii	1995	Mouse, vole	
B. taylorii	1995	Mouse, vole	
B. doshiae	1995	Vole	
B. vinsonni berkhoffi	1996	Dog	
B. clarridgeiae	1996	Cat, Human	
B. tribocorum	1998	Rat	
B. alsatica	1999	Rabbit	
B. khoelerae	1999	Cat	
B. vinsonni arupensis	1999	Cattle, Human	
B. weissii	2000	Cattle, cat	

Cat scratch disease

Cat scratch disease (CSD) is the most common *Bartonella* infection worldwide.[1] In patients with history of cat contact or scratches, the disease typically presents as a lymphadenopathy preceded by an erythematous papule at the inoculation site (Fig. 1). This cutaneous lesion develops 3–10 days after inoculation[3] and usually evolves through erythematous, vesicular, and papular crusted stages, persisting for about 1–3 weeks.[4] Hence, it may still be present as a crusted erythematous papule 2–6 mm in diameter when the regional lymphadenopathy develops 3–50 days after inoculation. The histopathology of the skin lesion is similar to the lymph node changes consisting of a diffuse inflammatory cell infiltrate associating numerous neutrophils and histiocytes admixed with scattered eosinophils and plasma cells. Epidermal hyperplasia and dermal deposits of proteoglycans may also be present in the skin.[5] Warthin-Starry silver stain frequently

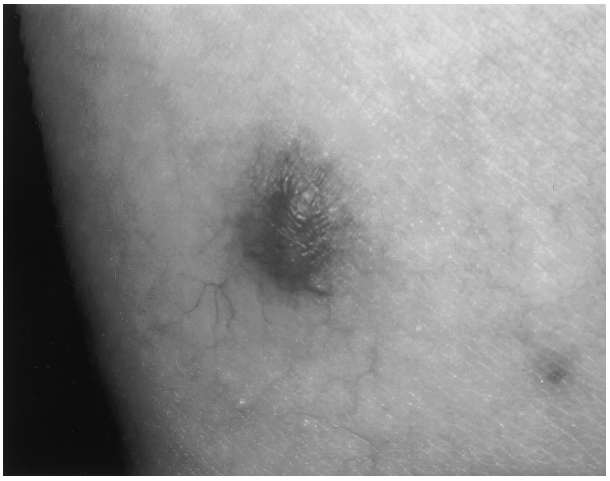

Figure 1 Cat scratch disease. Papular lesion at the inoculation site

reveals clustered bacteria within micro-abscesses, with progressive clearing of these micro-organisms as the lesion resolves.[5] Other, more unusual, skin manifestations include morbilliform eruptions, urticaria, erythema nodosum, erythema multiforme and erythema marginatum.

It is widely accepted that *B. henselae* is the primary etiologic agent of CSD.[6] Although it is currently impossible to reproduce CSD in a host other than the cat to fulfill the Koch's postulates, 'evidence of causation' for *B. henselae* was demonstrated in CSD using molecular biology.[7] However, two recent case reports identified *B. clarridgeiae* as the suspicious causative agent.[8,9] There have also been cases without evidence of *Bartonella* infection despite appropriate search. For example, when immunofluorescence assay was applied to serum from patients with the most strictly defined CSD cases, 5–15% of these samples yielded negative results.[10] Finally, the role of *Afipia felis*, initially considered to be the cause of CSD, is not ruled out, it being possible that this and other bacteria may be involved in a small percentage of CSD cases.[6]

Trench fever

In the past, trench fever was one of the most widespread bartonelloses. Transmitted by the body louse, the disease became rare after World War II, but surged again during the last decade in poor, homeless, alcoholic men living in urban areas.[11] This disease, caused by *B. quintana*, follows a cyclic clinical evolution combining fever, malaise, chills, anorexia, sweating, headache, conjunctival injection, myalgias and arthralgias. About 80–90% of the patients present crops of erythematous macules or papules measuring 1 cm or less on the abdomen, chest and back.[2] These cutaneous manifestations have not been thoroughly studied using histopathology. As the condition is quite fleeting, it would be expected to demonstrate only minimal, if any vasculitis.[5]

Bacillary angiomatosis

The first case of bacillary angiomatosis (BA) was reported in an AIDS patient.[12]. Nearly 10 years later, *B. henselae* and *B. quintana* were demonstrated from cutaneous lesions and blood of affected individuals by direct cultivation and polymerase chain reaction (PCR)-amplification of specific gene sequences.[13]

AIDS-associated BA was most frequently seen when the CD4 count decreased to less than 100 cells/mm.[12,14] It was also described in immunocompromised cardiac and renal transplant patients[15] and in patients under chemotherapy for hematologic malignancies[16] as well as in apparently immunocompetent individuals.[17,18] Bacillary angiomatosis was identified in different tissues including skin, brain, bone, lymph nodes, gastrointestinal and respiratory tract and bone marrow.[4,15]

Epidemiological studies have shown skin lesions to be the most frequent clinical manifestation of the disease, ranging from 55% to 90% of cases.[14,19] It is noteworthy that the incidence of BA has been dramatically reduced since the introduction of AIDS tritherapy and prophylactic antibiotherapy. The typical lesion is solitary or dispersed all over the body. The reddish-purple papule about 1 cm in diameter (Fig. 2) and may be difficult to differentiate clinically from Kaposi's disease, epithelioid hemangioma and pyogenic granuloma,[6] making it mandatory to examine a skin biopsy to confirm the diagnosis. Other BA lesions present under different aspects including smooth, warty and pedunculated papules, as well as subcutaneous nodules and hyperkeratotic plaques. They are rarely ulcerated or bleeding.

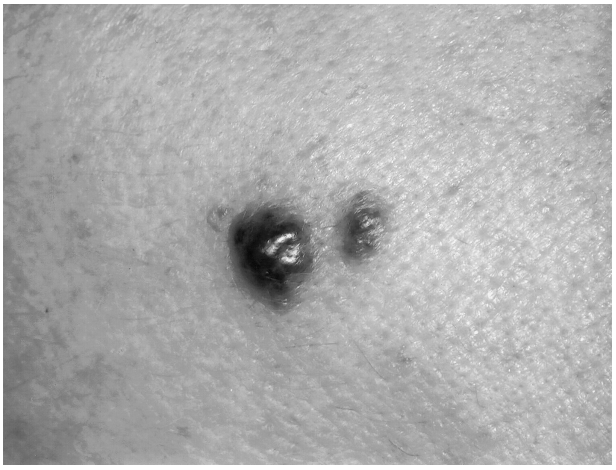

Figure 2 Bacillary angiomatosis in a cardiac transplant patient

Etiology

There is a current trend to curb the BA incidence, probably due to the extensive use of antimicrobial drugs as prophylactic agents in immunocompromised patients.[5] In the USA, BA is produced almost in equal proportion by *B. henselae* and *B. quintana*.[13,20] In contrast, *B. henselae* has only recently been identified in Europe as an agent causing the disease.[21] There is a lack of information about the causative organism(s) in the other continents. From the few reports available where serious efforts were made to identify the bacteria, there is at least one unsuccessful attempt; interestingly in two immunocompetent individuals with lesions histologically mimicking BA but lacking clumps of bacilli.[22] These findings leave an open door for searching for other *Bartonella spp*. or bacteria in BA lesions. The microbiological characterization of BA should be made, when possible, for understanding the BA etiology.

Pathophysiology

It is clear that BA is a consequence of assaults by body louse (*B. quintana*), cat scratch and cat fleas (*B. henselae*),[2] and there is evidence for *Bartonella spp*. ability to produce angiogenic factors.[23,24] Both micro-organisms have a similar

ability to produce cutaneous lesions but, while the latter is more prone to produce liver peliosis and lymph node disease, *B. quintana* is associated with a greater propensity to produce bony and subcutaneous lesions.[20] Liver peliosis is somewhat microscopically different from BA. This difference may reflect particular characteristics of this organ such as the proportion of epithelial to mesenchymal components and the vascular pattern.[25]

It is unclear why *B. henselae* produces CSD in some cases and BA in others, and why *B. quintana* produces diseases as distinct as trench fever, endocarditis and BA. It is obvious that an as yet unidentified immunological parameter of the host influences the different clinical manifestations of these bartonelloses. While the immune status clearly affects the clinical presentation, differences in virulence among various *Bartonella* strains may also be responsible for the varied disease presentations.[6]

Histopathology

The BA histological criteria are well defined.[22,26,27] The main salient features are a lobular accumulation of rounded blood vessels with plump endothelial cells. Cell necrosis, atypia and mitoses are especially found in densely cellular areas. A mixed inflammatory cell infiltrate with predominance of neutrophils and occasional leukocytoclasia is also present. Granular eosinophilic and Warthin-Starry-positive bacilli are the hallmark of the lesion. In addition, numerous Factor XIIIa's-positive dermal dendrocytes are present in BA.[28] There is indeed increasing evidence regarding the immunological activity of dermal dendritic cells and their interaction with the skin endothelium.[29] The large spectrum of angiogenesis-related factors[30] might also offer new research avenues in BA.

Verruga peruana

Detailed reviews have been presented about the etiology, pathogenesis, clinical presentation and treatment of verruga peruana.[31–34] *Bartonella bacilliformis*, the etiologic agent of the disease was the first identified member of the *Bartonella* genus. The disease is typically confined to Andean valleys of Peru, Colombia and the Equator, due to the ecologic distribution of its vector, the sand fly *Lutzomia verrucarum*.[31]

Verruga peruana is an eruptive angiomatous disease of the skin (Figs 3 and 4) that typically develops 2 months after an acute phase of bacteriemic disease known as Oroya fever or Carrion's disease. In addition to the casual presentation of the angiomatous lesions,[28,34,35] malignant-looking aspects have been identified.[36] There is a great histological similarity between the disease BA in HIV-positive individuals.[37] However, verruga peruana differs from BA at the microscopical level, at least by the lack of aggregates of bacilli (Table 2).

Actually, verruga peruana does not seem to be confined to the recognized epidemiological villages where it was originally documented anymore. We have indeed seen some cases of angiomatous lesions resembling verruga peruana in apparently immunocompetent individuals without any recognized risk factor including travel to verrucogenous areas and Oroya fever. As *Bartonella spp*. other than *B. bacilliformis* have been isolated from rodents in villages of Peru,[38] some of these angiomatous lesions with incomplete or absent epidemiological support could represent diseases caused by *Bartonella spp*. different from *B. bacilliformis*. On the other hand, there are no documented cases regarding the occurrence of diseases caused by *B. bacilliformis* in HIV-infected individuals. Finally, the immunodeficiency status associated with the majority of cases of BA, mainly CD4+ lymphocyte depletion and phagocytic dysfunction, could be compared with the immunological changes produced in the Oroya fever.[39] This could provide a suitable model of the influence of the immunological status on the development of some vascular lesions of the skin.

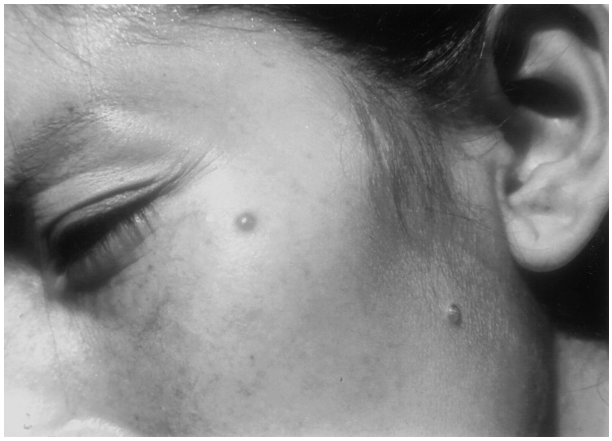

Figure 3 Verruga peruana. Two small papules on the face

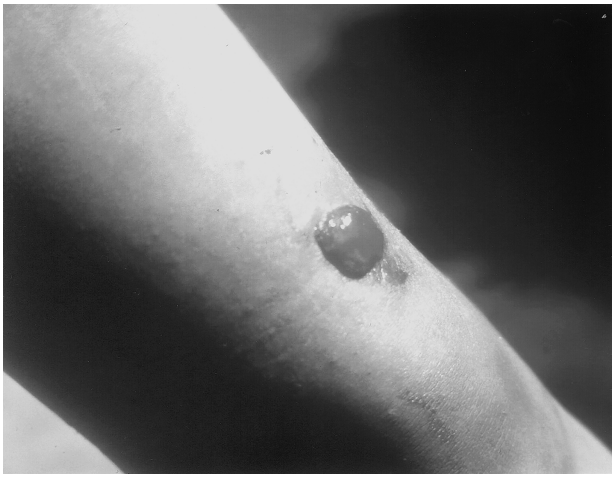

Figure 4 Verruga peruana, nodular type

Table 2 Similarities and differences between verruga peruana and bacillary angiomatosis

VERRUGA PERUANA	BACILLARY ANGIOMATOSIS
Etiology	**Etiology**
B. bacilliformis	*B. henselae, B. quintana, other Bartonella species?*
Epidemiology	**Epidemiology**
Confined to Andean valleys of Peru, Colombia and Equator	Worldwide distribution
Existence of an asymptomatic status carrier	No healthy carrier status proved in humans
Lutzomyia verrucarum is the sole vector known	Body louse(also head louse) is the vector of *B. quintana*
Animal reservoir not known but presumed	Cats, in particular kittens, are the reservoir of *B. henselae*
Monkey is the sole proved animal model for the eruptive phase of the disease	No animal model has been demonstrated for *B. quintana*
Clinical presentation	**Clinical presentation**
Usually a two-stage disease, preceded by an hemolytic phase followed by the eruptive one	Skin lesions occurring as papules, warts, pedunculated, subcutaneous nodules (rarely ulcerated or bleeding), or hyperkeratotic plaques
Natives are more prone to develop just the eruptive phase	Clinically these lesions look similar to verruga peruana
Foreign people usually develop devastating disease	
Immune status of the host	**Immune status of the host**
Impaired immunity in hemolytic phase of the disease with propensity to develop opportunistic infections	The vast majority of cases occurring in HIV-positive and other immunodeficiency status, however, there are reported cases in apparently immunocompetent individuals
Decreased CD4-T lymphocytes and augment of CD8-T lymphocytes in peripheral blood with inversion of the CD4/CD8 ratio	There is no information concerning the possible direct effect of *B. henselae* and *B. quintana* on the immune status of the host
Lesser degree of impaired cellular immune function	
Acute infection induces impaired immune function that precedes development of angiomatous lesions	
Natural history	**Natural history**
Skin lesions of verruga peruana regress spontaneously with little benefit of antibiotic therapy	Lesions resolve with antimicrobial therapy, better response in immunosuppressed individuals

Skin and the immune system in bartonelloses

The skin-restricted features of verruga peruana and the predominant skin manifestations in BA together with the immunological impaired status found in both diseases make it attractive to suggest a common pathobiological pathway. The skin might be a target of specific infectious agents responsible for angiomatous diseases in the setting of impaired immune function. Indeed, angiogenesis is a biological event strictly controlled and associated with wound healing, several chronic inflammatory diseases and tumor growth and metastasis.[40–43] The statement that *Bartonella*-associated vascular lesions may represent some variants of these angiogenic responses has already been made[44] and calls for further research. The ability of *Bartonella spp*. to produce angiogenic factors[24,44] might also be considered when analyzing the complex interaction between bacteria, skin cells and the immune system.

The immune function of the skin was emphasized many years ago under the concept of 'skin-associated lymphoid tissue' constituted by keratinocytes, Langerhans cells, T-cells and endothelial cells.[45] The biological interactions between cutaneous dendritic cells, endothelial cells and skin lymphocytes is altered in some pathological conditions. For instance, there is cumulated data related to the biology of the skin in HIV-disease[46–49] and the vascular proliferation in BA may represent a defect in the phagocytic function and development of granulomatous reactions such as those found in CSD.[50] In addition, *B. bacilliformis* tropism for the skin could be caused by the better growth of the bacilli at lower temperatures with dermal dendrocytes also playing a role.[28,50]

Conclusion

Bartonella spp. infections are responsible for different clinical presentations including vascular growths in the skin. Further research must be guided in order to identify the whole spectrum of the pathogens, in particular *Bartonella spp*. responsible for vascular lesions. The cellular and molecular components of BA and verruga peruana lesions should be scrutinized. Some analogy among these diseases could provide evidence for common biological mechanisms.

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