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1273 8.6.44 Bartonella bacilliformis infection and coccoid in the convalescent stage. B. bacilliformis can infect red blood cells (Fig. 8.6.44.2), endothelial cells of capillaries, and sinus- oidal lining cells. The organism is 2–3 µm long and 0.2–2.5 µm thick. In cultures, 1–10 flagella, 3–10 µm long, may originate from one end of the organism. Bartonella can be cultured in Columbia agar sup- plemented with 10% defibrinated sheep blood at 29°C under aer- obic conditions for up to 6 weeks. Multilocus sequence typing of Peruvian isolates of B. bacilliformis showed wide genetic diversity. While seven of the eight sequence types were closely related, one exhibited profound evolutionary divergence suggesting that it might represent a new Bartonella genospecies. Epidemiology Bartonellosis has occurred since pre-Columbian times, as proven by artistic representations in pre-Inca pottery and lesions in an an- cient mummy. It is an endemic disease mainly in inter-Andean val- leys in west, central, and east Andean areas of Peru (Fig. 8.6.44.3) and increasingly in

Amazonian areas where alternative arthropod vectors have been suggested (i.e. ticks). In Ecuador, bartonellosis is endemic in several areas (Loja, Zamora-Chinchipe) but with spor- adic clinical cases. This has suggested the existence of attenuated or less virulent strains. Knowledge of the epidemiology of Bartonella is incomplete but studies suggest that transmission is unstable and geographically highly heterogeneous with prevalence and incidence rates that vary considerably in time and space (Fig. 8.6.44.4). The transmission is influenced by the highly variable human behaviour and the environment, heavily influenced by climatic factors that de- termine changes in the abundance and behaviour of the vectors. The epidemiological pattern is endemic plus epidemic in the new areas. Transmission is usually in rural towns and around human dwell- ings. The disease occurs between 500 and 3200 m above sea level. Transmission varies throughout the year, being greatest towards the end of the rainy season (March to May). Interepidemic periods occur every 10–15 years. In endemic areas the infection has cluster distribution where approximately 80% of cases are concentrated in 20% of the houses. The risk of acquiring the disease is substantially higher (2.6 times) when a family member has a confirmed diagnosis of bartonellosis. The disease is most common in children under 15 years and for each year of life the risk of acquiring the disease decreases by 4%. Incidence is greatly influenced by climatic, envir- onmental, and ecological changes such as the El Niño phenomenon. At present, 11 species and subspecies of the genus Bartonella have been associated with human infections but only three have epi- demiological importance: B. bacilliformis, of which eight antigenic variants have been described in Peru; B. henselae, the major cause of cat-scratch disease and peliosis (Chapter 8.6.42); and B. quintana (formerly Rochalimaea), the agent of trench fever (Chapter 8.6.42). Recently, a new bartonella named B. ancashensis has been isolated from two patients with the verruga form. Other bartonellas such as B. rochalimae, B. vinsonii subsp. berkhoffii, B. vinsonii subsp. aru pensis, B. elizabethae, B. koehlerae, B. alsatica, B. grahamii, and B. clarridgeiae occasionally cause disease in humans. In immuno- compromised people, especially those with the HIV/AIDS, B. hense lae and B. quintana cause opportunistic infections, frequently manifested as cutaneous bacillary angiomatosis, resembling verruga peruana. The genus Bartonella is a unique pathogenic bacteria known to invade red blood cells. In endemic areas, in a high transmission period (1997–1998) the incidence rate was 12.7 person-years and 20.5% of those patients infected with B. bacilliformis remained asymptomatic, 31.5% devel- oped the eruptive form (chronic phase) without evidence of an acute illness, and 37% developed the eruptive form preceded by some symptoms. Only 11% will developed the classic acute form, with a higher frequency in children. However, these proportions tend to shift during periods of low transmission with increase of asymptom- atic infections. Outsiders generally develop acute severe forms of the disease (Oroya fever). Large epidemics have occurred when large groups of nonresidents have entered endemic areas. In 1870, an epi- demic engulfed workers building the railroad from Lima to Oroya (Fig. 8.6.44.5); it was estimated that there were 7000 deaths. Infection results from the bite of females of several species of sandflies (Lutzomyia), especially Lutzomyia verrucarum. These vectors frequent human dwellings and, because they are active during twilight hours, humans are infected around sunrise and sunset. Although the reservoir is unknown, humans are regarded as being increasingly important. Little is known about asymptom- atic carriage, but this may have a significant role in perpetuation
Fig. 8.6.44.1 B. bacilliformis in blood smear stained with Giemsa. Fig. 8.6.44.2 B. bacilliformis in a red blood cell.

 of transmission of infection in endemic areas. To date all studies in domestic and wild animals have been negative for B. bacilliformis. Pathogenesis After inoculation

of B. bacilliformis by a sandfly bite, the bac- teria multiply in endothelial cells of small vessels and phago- cytic cells near the skin. Systemic invasion and multiplication in endothelial cells and red blood cells follows. In the most serious cases, 95% of red cells are infected with numerous bac- teria. The hallmark of the disease is the severe haemolytic anaemia caused by massive infection of red blood cells and subsequent erythrophagocytosis. Several mechanisms con- tribute to anaemia: increased fragility, form and size alteration, and reduced half-life of infected and noninfected red cells. Some inhibition of haemoglobin synthesis, probably induced by toxic factors, has also been invoked, since red cell produc- tion increases dramatically with reduction of bacteraemia. Erythrophagocytosis contributes to lymphadenopathy and hepatosplenomegaly. 'Blockade' of the mononuclear phagocytic system and the presence of the circulating iron leads to super- infection, usually by enterobacteria, during the anaemia stage or early recovery from it. Transient depression of cellular immunity Fig. 8.6.44.3 Endemic area for bartonellosis; near Tarma, Peru. Copyright D. A. Warrell. 2000 2006 2012 2018 Fig. 8.6.44.4 Changes of the geographical distribution of bartonellosis in Peru between 2000 to 2018.

1275 has been reported. During the anaemic phase, mild lymphopenia with a reduction of CD4, a mild increase of CD8, and decrease of the polyclonal stimulation of lymphocytes occurs. High levels of interleukin (IL)-10 were found in the acute phase. In Gram-negative sepsis, an uncontrolled production of IL-10 may produce 'immunological paralysis' of antigen-presenting cells. The eruptive form appears a few weeks to months after the acute illness has subsided, and in Peru is named 'verruga peruana' (Fig. 8.6.44.6a, b). The vascular skin lesions show endothelial pro- liferation and histiocytic hyperplasia (the cells contain degenerate organisms; see Fig. 8.6.44.7) and later show fibrosis and necrosis. Electron microscopy of verrucous tissue shows B. bacilliformis in the interstitial tissues, indicating that the presence of the bacteria is important for this unusual vascular response to occur. Verruga peruana results from persistent infection, an immune response that is probably insufficient, and a peculiar vascular reaction, which could be caused by an angiogenic bacterial factor. In endemic areas recurrences are not rare (~ 5%). Clinical features The disease has two stages, anaemic and eruptive, with an asymp- tomatic intermediate period. After an incubation period of around 60 days (range 10–210 days), nonspecific prodromal symptoms ap- pear. The onset is usually gradual with malaise, mild chills, fever, and headache. Occasionally, high fever may develop rapidly or build up over a few days. It is accompanied by sweating and rigors. Common symptoms include weakness, aching of the head, back, and extrem- ities, prostration, and depression. The classical clinical picture is dominated by severe (haemolytic) anaemia and the patient rapidly becomes pale (Fig. 8.6.44.8), dyspnoeic, and jaundiced. There might be hepatosplenomegaly, generalized lymphadenopathy, tachy- cardia, myocarditis (Fig. 8.6.44.9), purpura, hepatitis, diarrhoea, pericardial effusion, exudates, anasarca, and retinal changes (Fig. 8.6.44.10); sometimes there is generalized oedema, drowsiness, and convulsions, and exceptionally meningoencephalomyelitis. The duration of this state is variable (generally 2–4 weeks). In pregnant women, the disease in this phase may cause abortion, fetal death,
Fig. 8.6.44.5 Endemic area for bartonellosis; Rimac valley, Peru—Puente Verrugas. Copyright D. A. Warrell. (a) (b) Fig. 8.6.44.6 Verruga peruana: miliary haemangioma-like lesions. 8.6.44 Bartonella bacilliformis infection

 and transplacental transmission of the disease; maternal death is common. Between 9 to 18% patients develop the classical symptoms (fever, anaemia, and jaundice) and 82 to 91% develop fever alone. In the intermediate period, patients are

asymptomatic and re- cover from the anaemia through increased bone marrow activity. This pre-eruptive period varies from weeks to months. In the eruptive stage, many nodular lesions of varying size appear on the face, trunk, and limbs over a period of a month or more and usually persist for 3 or 4 months. There is accompanying mild arth- ralgia, myalgia, and sometimes fever. The red or purplish skin le- sions are papules a few millimetres across. Most often the eruption is miliary (miliary form) with many haemangioma-like lesions of the dermis (Fig. 8.6.44.6a, b). Nodular lesions (nodular form) are larger but fewer and more prominent on the extensor surfaces of arms and legs (Fig. 8.6.44.11a, b). They are painless and prone to bleeding (Fig. 8.6.44.11c), secondary infection, and ulceration. The appear- ance can resemble haemangioma, cutaneous bacillary angiomatosis, granuloma pyogenicum, Kaposi's sarcoma, fibrosarcoma, leprosy (histoid form), or yaws. Occasionally one to a few, large, deep-seated ulcerating lesions (mular form) might develop. These tend to appear near joints where they can be painful and limit motion. Apart from skin, the mucous membranes of the mouth, conjunctiva, and nose, serous cavities, and the gastrointestinal and genitourinary tracts might be involved. The eruptive phase frequently tends to heal spon- taneously, although the course is often prolonged. A few patients de- velop a severe eruptive form, with dozens of bleeding and necrotic lesions which tend to become secondarily infected. The severe acute form can develop infectious and/or noninfectious complications. The principal complication is superinfection leading to septicaemia, which occurs at different stages of the disease but generally in the later part of the anaemic stage and during the inter- mediate stage. Formerly, salmonella, Mycobacterium tuberculosis, and Enterobacter were the most frequent pathogens. Reactivation of toxoplasmosis, histoplasmosis, pneumocystosis, leptospirosis, ty- phus fever, and staphylococcal infections are some of the other in- fections that are now frequent. A few patients develop the following syndromes: febrile haemorrhagic or ictero-haemorrhagic fever; acute respiratory distress or acute neurological symptoms (convul- sions, meningeal signs, hemiparesis, anisocoria, coma). Refractory Fig. 8.6.44.7 Verruga peruana: histology. Fig. 8.6.44.8 Severe anaemia (haematocrit 9%) in a patient with acute bartonellosis. Copyright D. A. Warrell. Fig. 8.6.44.9 Cardiomegaly due to myocarditis in a patient with acute bartonellosis. Copyright D. A. Warrell. Fig. 8.6.44.10 Retinal changes in bartonellosis.

1277 haemodynamic failure, severe respiratory distress, and renal failure are some of the noninfectious complications. Diagnosis Two elements must be considered: (1) travel or residence in an en- demic area and (2) a compatible clinical picture with demonstration of the bacteria in the blood film (Fig. 8.6.44.1). Fluorescence anti- body test, indirect haemagglutination, immunoblot (94% sensitive to chronic form and 70% sensitive to acute form), enzyme-linked immunosorbent assay (ELISA) and polymerase chain reaction (PCR) are new tests that are not generally available. PCR can de- tect B. bacilliformis-specific DNA from blood samples as well as skin biopsies. Antibodies are nonspecific due a cross-reaction with B. henselae, B. quintana, Chlamydia psittaci, and unknown antigens. The differential diagnosis in people living in endemic areas in- cludes: leptospirosis, rickettsioses, toxoplasmosis, P. vivax malaria, and louse-borne relapsing fever. Laboratory features Bartonella can be isolated from the blood during the anaemic stage and sometimes during the eruptive stage. The sensitivity of blood smear detection varies with the phase of the disease: 90% are positive during the acute phase, less than 10% in the verrucous phase and less than 1% in asymptomatic people. The specificity of blood smears varies from 75 to 98% and the positive predictive value is 71–94%. The enriched media might be positive in 4 to 28 days at 28°C. As fever develops, intraerythrocytic bacteria are visible in thick and thin films stained with Giemsa's, Wright's, or other Romanovsky stains. Organisms can also be seen and cultivated in verrucous skin lesions. PCR is the best method to detect asymptomatic infection. The

anaemia can be very severe (haematocrit <10%). It is haemo- lytic but Coombs' test negative. The blood picture is of a macrocytic and hypochromic anaemia with polychromasia, anisocytosis, and poikilocytosis. Reticulocytosis is marked (average 11%). The marrow is hyperactive and megaloblastic with erythrophagocytosis. The white cell count is not markedly elevated unless there is a secondary infec- tion. Thrombocytopenia is quite common. After the crisis, the intra- cellular organisms become coccoid and later disappear, the white cell count rises, and there is lymphocytosis. Eosinophils, which are usu- ally absent during the acute stage, reappear in the peripheral blood. Prognosis Deaths usually occur during the anaemic phase. In the preantibiotic era, case fatality varied between 20 and 95%. At present, it varies between 1.1 and 2.4% in endemic areas and around 9% in patients admitted to hospital. During outbreaks, especially when the disease (a) (c) (b) Fig. 8.6.44.11 Verruga peruana: nodular haemangiomatous lesions. 8.6.44 Bartonella bacilliformis infection

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