The pathophysiology of the acute phase of human bartonellosis resembles AIDS

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Background

Human bartonellosis, or Carrion’s disease, is an endemic anthroponosis described only in South America [1]. The disease is caused by Bartonella bacilliformis, an intracellular gram negative rod transmitted by the bite of mosquitoes belonging to the genus Lutzomyia [2]. Several other species of Bartonella (Bartonella quintana, Bartonella henselae, B. elizabethae) can cause disease in humans, but none of them causes immunosuppression by itself as B. bacilliformis does. Bartonellosis is a biphasic disease, characterized by an initial, acute stage of fever and severe anemia; and a late phase presenting with benign vascular tumors known as “verruga peruana” or “peruvian warts” [1].

Bartonellosis has been recognized in South America since before the arrival of the European invaders. In fact, pre-columbian ceramics depict human figures affected with prominent verrucous lesions [3]. The first medical description of the disease by Tomas Salazar dates from 1858 [4]. The eponymous name “Carrion’s disease” honors Daniel A. Carrion, a Peruvian medical student who inoculated himself with material from a verrucous lesion [5]. Although he eventually died from the acute form of the disease, his efforts were the first tangible demonstration of the biphasic nature of the disease. In 1905, Alberto Barton described B. bacilliformis invading red blood cells. B. bacilliformis is the only bacterium that parasitizes red blood cells [6], and in 1926 Hideo Noguchi was the first to culture it in the laboratory [7].

B. bacilliformis is a facultative intracellular, aerobic gram negative bacilli or cocobacilli that measures 2–3 mm in length and 0.2–0.5 mm in width. It belongs to the genus Bartonella. The previously named Rochalimae (B. quintana, B. hensalae, B. elizabethae) and Grahameella have been regrouped in this genus [8,9].

Human bartonellosis has been described in Ecuador and Colombia [10], but the majority of cases occur in Peru. The disease has reemerged in Peru during the last decades, with a geographic distribution, extending from the western slopes of the Andes, to the Peruvian coastline and to the upper regions of the Amazon jungle [11,12].

Humans are the only reservoir of bartonellosis, and the main vector is Lutzomyia verrucarum townsendi, although other Lutzomyia species have also been described [2].

The incubation period usually lasts 60 days following a mosquito bite, but it may range between 10 and 270 days. B. bacilliformis first invades the endothelial cells of capillary vessels and then secondarily parasitizes red cells [13]. The red blood cell and intraerythrocytic Bartonella are then phagocytized by...
macrophages. The destruction of red blood cells manifests as hemolytic anemia; the thrombosis of small vessels causes end-organ ischemia; the erythropagocytosis generates hyperplasia of the reticulo-endothelial system including lymphadenopathy and organomegaly; and the release of inflammatory cytokines manifests as fever, malaise, anorexia, headache, arthralgias, back pain and somnolence. Acute bartonellosis accounts for all the lethality of the disease, which can be as high as 90% in untreated cases [14].

The chronic phase of the disease manifests with either vascular verrucous lesions – several months after the acute event – or asymptomatic, chronic bacteremia. The verrucous lesions are indolent and tend to resolve spontaneously after several months or after only weeks with antibiotic treatment [15].

Bartonella has been traditionally treated with chloramphenicol, because of its activity against both Bartonella and the most common secondary pathogen Salmonella spp. [14], however amoxicillin–clavulanate and ciprofloxacin are contemporary treatments recommended by experts [16]. Bartonella is also highly susceptible in vitro to many other antibiotics such as aminoglycosides, rifampin, tetracycline and trimethoprim-sulfamethoxazole [17].

During the acute phase of bartonellosis a high frequency of opportunistic infections, many of them similar to the ones seen in AIDS, may complicate the course of the disease. Salmonella is the most common agent causing superinfection, but other organisms have been reported: Toxoplasma gondii, Histoplasma capsulatum (disseminated histoplasmosis), Staphylococcus aureus (sepsis), Enterobacter sp., Shigella dysenteriae, Pseudomonas aeruginosa, Pneumocystis jiroveci, Mycobacterium tuberculosis and Plasmodium vivax [1,14].

Along with opportunistic infections, there are a number of other complications in human bartonellosis that cannot be directly explained by the hemolytic anemia or the microvascular thrombosis induced by the bacteria. We speculate that they are manifestations of an immune reconstitution inflammatory syndrome (IRIS) similar to the one extensively described in the AIDS literature [18]. IRIS is not the exclusive domain of HIV-infected patients. It has also been described as:

- “Paradoxical reaction” in tuberculosis and “reverse reaction” in leprosy, both manifested by worsening of symptoms after initiation of a specific treatment [19,20];
- Immune reconstitution of transplant patients once immunosuppressant therapy is weaned off [21]; and
- Immune reconstitution during the puerperium, after the pregnancy-induced immunosuppression resolves and diseases are unmasked [22].

HIV-associated IRIS is the clinical deterioration of either a latent or preexisting opportunistic infection, or of a non-infectious condition, despite increased CD4+ T cell lymphocyte counts and decreased plasma HIV viral loads [23] following the use of antiretroviral therapy. HIV-associated IRIS can be understood as the appearance of new symptoms in a patient with sub-clinical disease, i.e. an unmasking of an anti-inflammatory reaction to replicating organisms; or as a paradoxical worsening of a preexisting sub-clinical disease, i.e. a reaction to dead organisms or antigens [24]. Several attempts to establish a case definition for IRIS have been made, although none has reached a consensus [25–28]. Nevertheless, confirmation of HIV infection; evidence of immune reconstitution such as elevation of the CD4+ T cell count or declining HIV viral load; atypical presentation of symptoms; and exclusion of alternative explanations for clinical deterioration such as drug resistance, poor adherence to treatment or drug toxicity are recurrent themes among the proposed definition criteria [18,24,25].

In human bartonellosis, a number of complications may have one or more of the following characteristics:

- They occur subacutely, during the course of the disease.
- They occur in the absence of microbiological evidence of persistent Bartonella infection.
- They seem to respond well to steroids.

Those conditions are: neurobartonellosis, subacute pericardial effusions and subsets of thrombocytopenic purpura [29–31]. We believe they represent IRIS manifestations following antibacterial treatment.

Although previous studies have described the immunosuppressive effect of human bartonellosis [32,33] none has suggested a parallelism between human bartonellosis and HIV infection. An article published in this journal in 1997 [33], proposed that L-forms of Bartonella spp. (not specifically B. bacilliformis), i.e. bacterial forms of slow progression induced by the use of antibiotics, may contribute to the clinical progression of AIDS. According to the referred article [33] the L-forms might be confused with HIV virions in pathological samples or be missed altogether because they resemble artifacts or necrotic debris. However this hypothesis has never been proven. L-forms of B. bacilliformis have been observed in vitro [34], but to our knowledge they have never been proven in vivo. Furthermore although some species of Bartonella (B. quintana and B. henselae) are known to cause infections in HIV-infected patients – such as bacteremia, bacillary angiomatosis and peliosis hepatis – there has never been a description of coinfection with B. bacilliformis and HIV.

Hypothesis

The clinical course of human bartonellosis resembles AIDS. In both conditions similar opportunistic infections occur as a consequence of immunosuppression. An immune reconstitution inflammatory syndrome is responsible for the clinical worsening or atypical clinical manifestations after appropriate antimicrobial therapy is instituted.

Evaluation of the hypothesis

There are several prominent similarities between human bartonellosis and AIDS (Table 1). First, in both there is a decline in cellular immunity. The CD4+ T lymphocytes are the main target of HIV infection, and their decline below the threshold of 200 cells/μl fulfills the criteria for the diagnosis of AIDS [35]. Similarly, in bartonellosis the presence of opportunistic infections during the acute stage has been attributed to immunological changes in the host, which may include a significant reduction in T lymphocytes [32]. An anergic state with lack of immune response both to unspecific antigens and to a preparation of verrucous granuloma was reported as early as 1926 [36]. A marked decrease in the CD4+ T lymphocytes and an inversion of the CD4+/CD8+ ratio was reported in the 1980s [32]. The B lymphocytes were unaffected and there was a good humoral response, with production of antibodies that could prevent the invasion of new erythrocytes. More recent studies have failed to prove abnormalities in the CD4+ or CD8+ cell counts, however they showed increases in the levels of interferon-gamma and interleukin-10, similar to the ones seen in sepsis [37]. The immunologic reaction in acute bartonellosis occurs at a very fast pace, and may look different depending on when it is measured. Thus the variability of reported cellular immune responses may vary from one experiment to the other due to such factors as serum sampling time, antibiotic use, or infectious bacterial load. II–10 may be pivotal in the pathophysiology of human bartonellosis: this cytokine suppresses both macrophage and dendritic cell function by inhibiting MHC class II and B7–1/B7–2 costimulatory molecule expression, and also by limiting the
production of pro-inflammatory cytokines (IL-1, IL-6, IL-12, IL-18, and TNF–α) and chemokines (MCP1, MCP5, RANTES) [38]. In milder Bartonella infections, the anti-inflammatory effects of IL-10 may limit the harm to the host, at the cost of allowing persistent infection and thereby favoring onward transmission [39]. In more severe Bartonella infections, the production of IL-10 may be unable to match the strength to the pro-inflammatory response, thus failing to control the infection and becoming associated with higher mortality [40]. In summary, in both AIDS and bartonellosis, a decline in the cellular immunity is responsible for the clinical manifestations of the disease, either by a decrease of CD4+ T cells or through macrophage dysfunction. In bartonellosis, macrophage dysfunction causes septic syndrome, both directly associated with bartonellosis, and by predisposing to opportunistic infections.

The second resemblance between AIDS and bartonellosis is the striking similarity in opportunistic infections. Acute bartonellosis can be complicated by infections caused by colonizing extracellular bacteria such as S. aureus or Salmonella spp., both of which are known to be more prevalent among HIV-infected patients [14,35,41]. Many other opportunistic infections are caused by reactivation of latent foci of intracellular organisms as a consequence of the decline in cellular immunity. Intracellular opportunistic infections described in both AIDS and bartonellosis include: tuberculosis, toxoplasmosis, histoplasmosis, salmonellosis, Pneumocystis jirovecii pneumonia and herpetic eruptions [1,14].

We also see parallels between the HIV-associated IRIS and several of the manifestations of bartonellosis. Below we present a description of neurobartonellosis, pericardial effusion and thrombocytopenia. All of these conditions may occur in the absence of Bartonella organisms, they may not be prevented by the use of antibiotics, and they seem to coincide with an improvement of the patients’ cellular immunity. In a similar fashion HIV-associated IRIS occurs with evidence of decrease of the HIV viral load, is not prevented but rather favored by the use of antiretroviral therapy, and coincides with an rise in CD4+ T cells.

Neurobartonellosis is a condition rarely described outside the Peruvian medical literature; nevertheless it occurs in as many as 11–27% of individuals during the acute hemato phase and it is associated with a lethality rate ranging from 30% to 60% [42]. The manifestations include altered mental status ranging from somnolence and confusion to coma, seizures, and meningeal signs. Analysis of the CSF reveals mild mononuclear pleocytosis with normal glucose and protein, and negative stains and cultures for Bartonella [14]. Neurobartonellosis appears late in the course of the disease or after an initial clinical recovery and negativization of peripheral smears following administration of antibiotics [29].

Cardiovascular manifestations of bartonellosis, such as congestive heart failure, acute pulmonary edema and cardiogenic shock are usually due to severe anemia, and were described initially by Odriozola, more than a century ago [43]. More recently, pericardial effusions that can rapidly evolve into pericardial tamponade have been described in 44% of patients with cardiovascular complications [30]. These effusions may appear acutely or subacutely. Acute effusions are most likely due to direct invasion of Bartonella of the pericardium, or less frequently due to associated Toxoplasma myocarditis [14]; however the subacute effusions are an inflammatory process with negative microbiologic studies for the presence of Bartonella [30].

Thrombocytopenic purpura manifesting with petechiae, ecchymoses, epistaxis, gingivorrhagia, or gastrointestinal bleeding occurs in 10–26% of patients during the acute hematic phase [42,44]. In many cases, thrombocytopenia is caused by disseminated intravascular coagulation associated with Bartonella bacteremia and severe sepsis. However, there is a distinctive group of clinically stable patients who develop thrombocytopenia that does not require transfusion and that responds well to the use of corticosteroids [31].

Although the host immunity is crucial for control of infections, an exaggerated immune response induced by the use of antiretroviral therapy, or in our case by the use of antimicrobials, may actually be detrimental to the host [28].

The pathogenesis of HIV-associated IRIS remains poorly understood. In granulomatous infections such as tuberculosis, the most common and most studied disease unmasked or exacerbated by IRIS, the main emphasis has been on the rise in CD4+ T cells, particularly the subset of CD4+CD25+Foxp3+ Treg cells – or memory cells – and the subsequent imbalanced effect on regulatory cellular immune responses against pathogen-specific antigens [18]. However, Lawn has described that IRIS often occurs within the first weeks after the initiation of antiretroviral therapy, before any substantial increment in the CD4+ T lymphocyte count occurs [45]. Hence, other authors have proposed that an excessive activation of previously dysfunctional macrophages in the presence of a mycobacterial antigen may explain the clinical manifestations of IRIS [46]. In other words, the role of the macrophage in the pathogenesis of IRIS might be more prominent than previously thought. Similarly, we believe that in human bartonellosis, antibiotic treatment causes a decrease of the bacterial antigenic load and an exaggerated recovery of macrophages’ phagocytic function, forming the pathophysiologic basis of neurobartonellosis, subacute pericardial effusion and of a subtype of thrombocytopenic purpura.

The following paragraphs and Table 2 summarize the pathogenesis of human bartonellosis as we understand it. Of course, these processes occur very rapidly, in a matter of hours or days, as compared with the pathogenesis of HIV-associated IRIS which takes days to weeks:

### Table 1
Comparison of pathophysiologic characteristics between AIDS and human Bartonellosis.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>AIDS</th>
<th>Bartonellosis</th>
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<tbody>
<tr>
<td>Decline of cellular immunity</td>
<td>Yes, predominantly by decrease and dysfunction of CD4+ T cells</td>
<td>Yes, probably by dysfunction of macrophages</td>
</tr>
<tr>
<td>Associated opportunistic infections</td>
<td>Tuberculosis, toxoplasmosis, histoplasmosis, Pneumocystis jiroveci, herpes</td>
<td>Tuberculosis, toxoplasmosis, histoplasmosis, Pneumocystis jiroveci, herpes</td>
</tr>
<tr>
<td>Decrease of antigenic load following treatment</td>
<td>Decrease of HIV viral load following initiation of antiretroviral therapy has been documented</td>
<td>Decrease in the Bartonella load has not been documented following antimicrobial therapy, however the appearance of complications despite absence of organisms and appropriate treatment, is highly suggestive of this trend</td>
</tr>
<tr>
<td>Improvement of cellular immunity following treatment</td>
<td>Yes, most of the time subacutely, but immune reconstitution can occur as soon as two weeks after starting antiretroviral therapy</td>
<td>Yes, probably as soon as 48–72 h after antibiotic treatment gets started</td>
</tr>
<tr>
<td>Improvement of clinical condition following use of specific anti-infective therapy and steroids</td>
<td>Yes, usually after few days</td>
<td>Yes, usually after few days (shorter time period as compared with AIDS)</td>
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Table 2
Pathogenic steps during the acute hematic phase in human bartonellosis.

<table>
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<tr>
<th>Steps</th>
<th>1</th>
<th>2</th>
<th>3</th>
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<tr>
<td>Proliferation of Bartonella inside endothelial cells and release into the general circulation</td>
<td>Phagocytosis of large number of erythrocytes by the macrophages of the reticuloendothelial system: spleen, liver, lymph nodes and bone marrow</td>
<td>Development of infections by colonizing bacteria (Staphylococcus, Salmonella)</td>
<td>Control of bartonellosis and opportunistic infections</td>
<td>Decrease in the Bartonella bacterial load</td>
<td>Reactivation of latent infections is patent</td>
<td>Interaction between free antigens of reactivated latent infections and specific memory cells</td>
</tr>
<tr>
<td>Immune deficiency</td>
<td>Macrophages are unable to participate in the immune response</td>
<td>Macrophages recover their ability to mount an immune response</td>
<td>Immune reconstitution</td>
<td>Immune reconstitution inflammatory syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antimicrobial therapy is able to control Bartonella infection, thus liberating macrophages from their situation of over activation and allowing them to recover their ability to mount an immune response</td>
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</table>

(1) Following a Lutzomyia bite, *B. bacilliformis* organisms invade endothelial cells, proliferate and get released to the general circulation.

(2) In severe infections almost 100% of the circulating erythrocytes become parasitized. The red blood cells are phagocytized by macrophages of the reticuloendothelial system causing generalized lymphadenopathy, hepatosplenomegaly and splenomegaly. This excessive macrophage activation causes a temporary dysregulation of the immune system and concomitant decrease of cellular immunity.

(3) The impairment of cellular immunity favors the reactivation of latent intracellular infections, preferentially tuberculosis and toxoplasmosis, which are common in the geographic area where human bartonellosis occurs. The macrophage dysfunction also enables replication of colonizing organisms such as *Staphylococcus* species and *Salmonella*.

(4) The patient manifests fever and anemia and receives antibiotic treatment.

(5) Antimicrobial therapy is able to control Bartonella infection, thus liberating macrophages from their situation of over activation and allowing them to recover their ability to mount an immune response.

Free antigens from opportunistic organisms, dead Bartonella, or from Bartonella previously “hidden” in endothelial cells (a known sanctuary of this organism) [47], interact with antigen-specific memory cells, which in turn recruit macrophages, favoring a generous inflammatory response with atypical clinical manifestations. In comparison to the HIV-associated IRIS – which tends to occur weeks after the initiation of antiretroviral therapy – the Bartonella-associated IRIS may occur abruptly, within hours of antibiotics initiation. Although in most cases an immunologic recovery pairs with a similarly potent inflammatory reaction, there is no linear dose–response relationship. Rather, the intensity of inflammatory response probably depends on previous exposure to Bartonella and on individual genetic predisposition. Patients affected with bartonellosis who do not live in endemic areas tend to have more severe manifestations of the disease [48]. Just as in the setting of HIV infection, herpes virus IRIS is associated with: HLA-B44, the major histocompatibility complex ancestral haplotypes HLA-A2, -B44, -DR4, and allele 1 at a single nucleotide polymorphism (SNP) in the 3′UTR of the IL12B gene encoding IL-12 p40, yet-to-be-identified genes may be associated with IRIS in the setting of bartonellosis [26].

In summary, we believe that AIDS and human bartonellosis share striking similarities. In both, dysregulation of the immune system causes a deterioration of the cellular immunity and predisposes to opportunistic infections. In both, treatment directed against the etiologic agent of the disease may induce immune reconstitution and favor the manifestation of atypical symptoms. Specifically, in human bartonellosis, the rapid restoration of phagocytic function and the massive cytokine secretion from macrophages may account for the manifestations seen in neuro-bartonellosis, subacute pericardial effusion and subsets of thrombocytopenic purpura. If this hypothesis proves correct, targeted courses of corticosteroids or other immunoregulatory drugs such as montelukast, or thalidomide may prove to be useful when dealing with these complications [49,50].

Conflicts of interest statement

None declared.

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