Bacillary angiomatosis in a HIV-negative patient

Irene Vivancos Koopman[1] BA, Ndanzia Mpunga[1] BA, Andrew Menezes[2] MD, Paloma Rivero-Moragrega[3] MD, Huma Siddiqui[4] MD, Jose Cadena-Zuluaga[3,5] MD, Patrick J. Danaher[3,5] MD, FACP, FIDSA, Chad Hivnor[6,7] MD, FAAD

Affiliations: [1]University of Texas Health Science Center San Antonio Long School of Medicine, San Antonio, Texas, USA, [2]South Texas Veterans Health Care System, Department of Medicine, San Antonio, Texas, USA, [3]University of Texas Health Science Center San Antonio, Division of Infectious Diseases, San Antonio, Texas, USA, [4]South Texas Veterans Health Care System, Department of Pathology, San Antonio, Texas, USA, [5]South Texas Veterans Health Care System, Department of Infectious Diseases, San Antonio, Texas, USA, [6]University of Texas Health Science Center San Antonio, Division of Dermatology, San Antonio, Texas, USA, [7]South Texas Veterans Health Care System, Department of Dermatology, San Antonio, Texas, USA

Corresponding Author: Ndanzia Mpunga, 7703 Floyd Curl Drive, San Antonio, TX 78229, Tel: 682-558-7427, Email: mpungan@livemail.uthscsa.edu

Abstract

Bacillary angiomatosis is a rare cutaneous manifestation caused by infection with *Bartonella henselae* that is most often seen in immunocompromised individuals, particularly those with HIV. We present an HIV-negative elderly man with bacillary angiomatosis with unexplained pancytopenia. The patient presented with a solitary, pedunculated, vascular nodule on his right forearm, and a shave biopsy was performed to rule out metastatic cancer. Biopsy results were consistent with bacillary angiomatosis, which was confirmed with polymerase chain reaction. Further evaluation revealed severely low *CD4* counts in our patient, despite two negative HIV tests and lack of immunosuppressive drugs or conditions besides cytopenia. He eventually met criteria for idiopathic *CD4* lymphocytopenia and was treated with doxycycline for coverage of possible disseminated infection. This case demonstrates the importance of keeping bacillary angiomatosis in the differential diagnosis in patients presenting with pedunculated angioproliferative lesions, regardless of HIV status.

Keywords: bacillary angiomatosis, disseminated disease, HIV-negative, idiopathic lymphocytopenia, immunodeficiency

Introduction

Bacillary angiomatosis, also known as epithelioid angiomatosis, is a rare cutaneous manifestation of infection with *Bartonella henselae* or *Bartonella quintana* [1]. It is characterized by angioproliferative lesions on the skin or internal organs and most commonly develops in immunodeficient individuals, particularly those with HIV or low *CD4+* lymphocyte counts [1]. Infection with *Bartonella henselae* is commonly associated with cat bites or scratches and often presents with lymphadenopathy [2,3]. Severe infections may cause persistent bacteremia, leading to the development of endocarditis, angioproliferative disorders, and encephalitis [2,4]. Clinical manifestations and the progression of the infection can vary between patients and correlate with the immune status of the individual [2]. Herein, we present a unique case of bartonellosis in an elderly HIV-negative patient with idiopathic *CD4+* lymphocytopenia.

Case Synopsis

A 74-year-old man presented to the dermatology clinic for a skin lesion after a referral from his primary care physician. He had multiple comorbidities including diabetes mellitus type 2, coronary artery disease, heart failure with preserved ejection

fraction, atrial fibrillation, pulmonary hypertension, chronic obstructive pulmonary disease, obstructive sleep apnea, a history of treated pulmonary *Mycobacterium avium* infection, and a long history of cytopenias. History was negative for previous dermatological conditions, and physical examination revealed a solitary mass on his right forearm that measured 1.3cm in diameter. The lesion had central eschar that bled easily with no exudate (**Figure 1**).

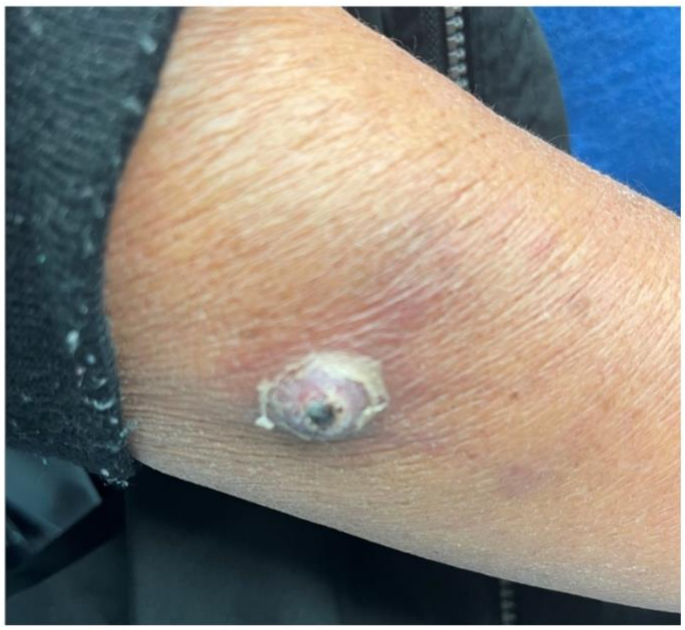

Figure 1. *Solitary, pedunculated, vascular nodule with a central eschar of the right forearm measuring 1.3cm in diameter.*

A shave biopsy was performed to exclude metastatic cancer owing to the vascularity and pedunculated character of the lesion. The pathology report described an ulcerated, inflammatory nodule with an epidermal collarette (**Figure 2**). The center of the lesion contained granulation tissue consisting of proliferative capillaries, acute inflammatory cells, and fibrinous exudate (**Figure 3A, B**). Additionally, the Gram and Warthin-Starry stains revealed only vague organisms, which were inconclusive for bacillary angiomatosis (**Figure 4A, B**). However, given the high suspicion for bacillary angiomatosis based on the clinical characteristics, polymerase chain reaction for *Bartonella* species. was performed, yielding a positive result. These findings were suggestive of bacillary angiomatosis and the patient was started on second-line therapy with azithromycin, 500mg daily, given a reported allergy to tetracyclines, the first-line agents. Upon further interview, the patient stated he had been caring for feral cats, which further supported this diagnosis. Pertinent laboratory findings included pancytopenia as well as very low *CD4+* and *CD8+* absolute counts dating back at least two years (153 cells/mL [323-1546 cells/mL] and 66 cells/mL [170-1154 cells/mL] in 2023, and 232 cells/mL and 40 cells/mL in 2020, respectively). Review of the record revealed intermittent cytopenias (with persistent lymphopenia) dating back to at least 1994. Flow cytometry of the peripheral blood during this presentation was not suggestive of leukemia. Further hematology evaluation was negative for nutritional deficiencies except mild iron deficiency that was determined an unlikely cause of his cytopenias. HIV testing was negative, including fourth generation enzyme-linked immunoassay during this presentation and multiple enzyme-linked immunoassays and polymerase chain reactions dating back to 1994.

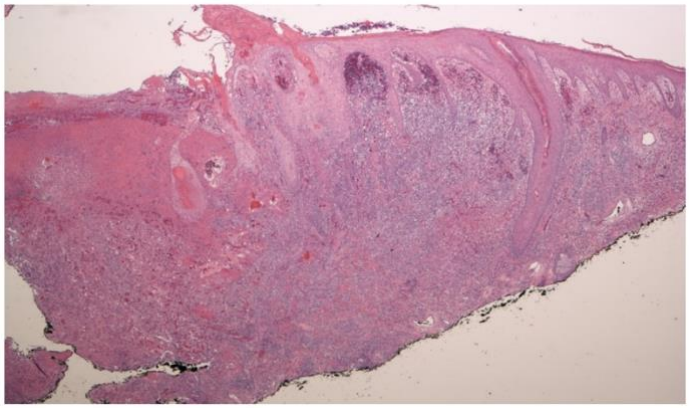

Figure 2. *4X hematoxylin and eosin showing keratoacanthoma-like lesion with peripheral epidermal collarette, central fibrinoid degeneration, and underlying reactive vascular proliferation with acute and chronic inflammation.*

A week after the nodule was biopsied, the patient was admitted to the hospital for worsening headaches, frequent falls, ataxia, confusion (trailing off in the middle of sentences and difficulty with word finding), and tremors, which had been present for about 6 months. His neurological exam was

notable for signs suggestive of parkinsonism: right hand resting tremor, stooped posture, bilateral upper and lower extremity bradykinesia, and slow shuffling gait with freezing on initiation. He was evaluated for possible *Bartonella* species. involvement in the central nervous system. Computed tomography and magnetic resonance imaging of the brain were unremarkable; cerebrospinal fluid protein, glucose, and cell counts were normal; no pathogens were detected in the cerebrospinal fluid by standard multiplex polymerase chain reaction (BioFire FilmArray meningitis/encephalitis panel, Biomerieux, Salt Lake City, UT, USA); no pathogens were detected in the cerebrospinal fluid by next generation sequencing (quantitative polymerase chain reaction + Next Generation Sequencing, MicroGenDX, Lubbock, TX, USA); cerebrospinal fluid antibody testing revealed *Bartonella henselae* titers of 1:4 for IgG and <1:1 for IgM (both IgG and IgM were <1:1 for *Bartonella quintana*). Blood cultures, polymerase chain reaction of blood, and serology for *Bartonella* species. were all negative. Carbidopa/levodopa was initiated at the recommendation of the neurology consultant.

At clinic follow-up about one month after initiation of azithromycin, the initial nodule on his right forearm was noted to have expanded and a new one was noted on his right medial buttock. His neurological symptoms were unchanged. Because of disease progression and inability for azithromycin to achieve significant concentrations in the cerebrospinal fluid, he underwent an oral graded challenge to doxycycline in clinic. He received an

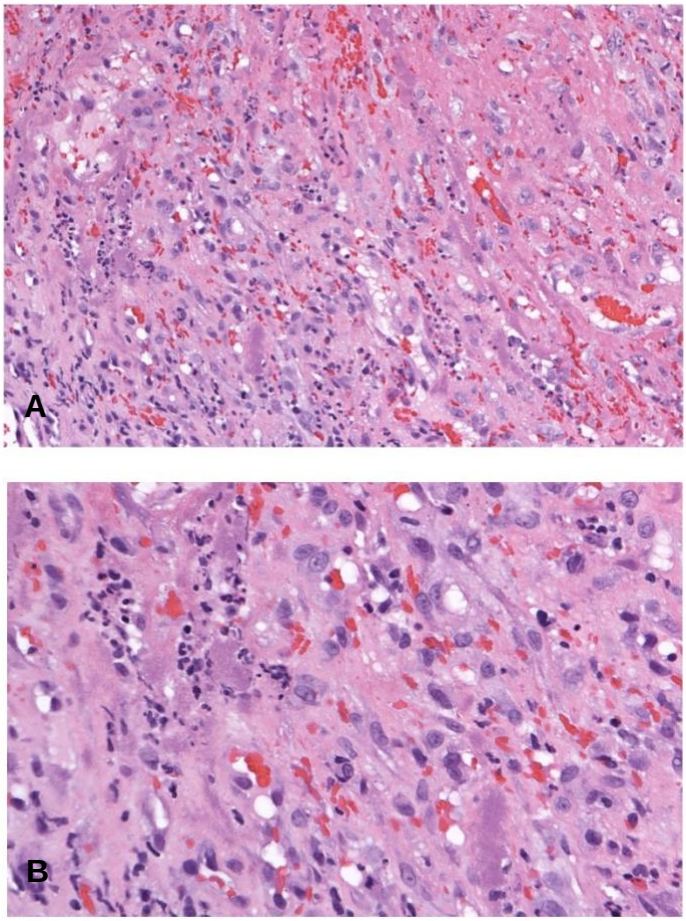

Figure 3. A) *20X hematoxylin and eosin showing vascular proliferation, with amorphic violet deposits surrounding blood vessels and acute inflammation.* **B)** *40X hematoxylin and eosin highlighting amorphic violet deposits surrounded by neutrophils.*

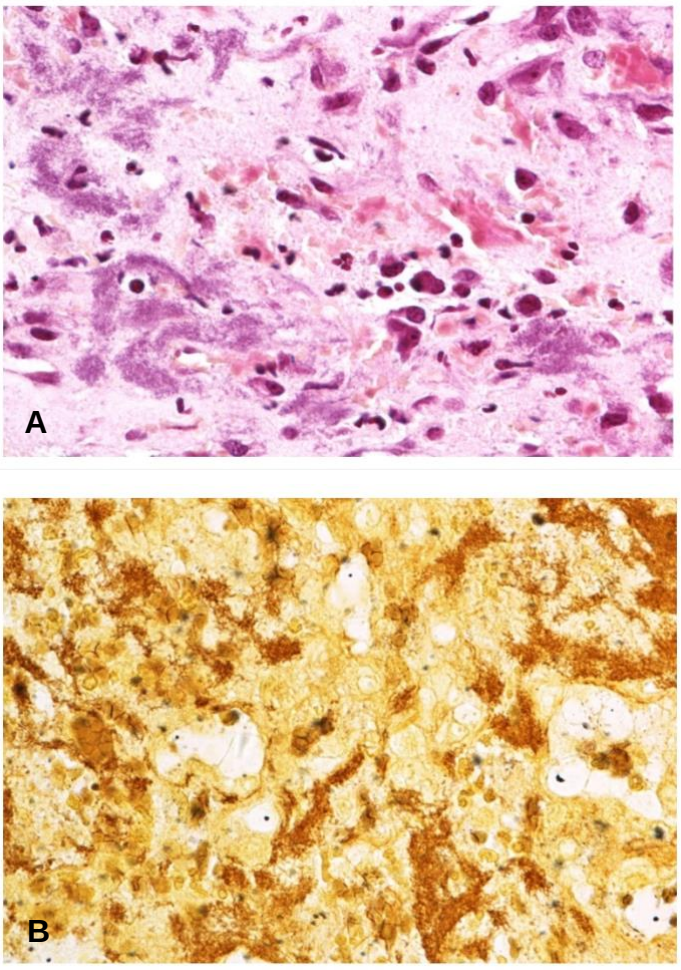

Figure 4. A) *Gram stain photomicrograph displaying gram negative rods in amorphic violet deposits.* **B)** *Warthin-Starry stain with inconclusive findings, but suggestive of bacillary organisms.*

initial dose of 10mg doxycycline and was closely monitored for signs of an allergic reaction such as urticaria, flushing, dyspnea, or dysphagia. No signs of allergic reaction were observed, allowing for an increased dose administration of 50mg doxycycline 30 minutes later. With no adverse effects, a final dose of 100mg doxycycline was given after another 30 minutes without complications. Following the successful challenge, his antibiotic regimen was switched from azithromycin to doxycycline 100mg twice daily.

At the time of writing, his skin lesions have resolved, and his central nervous system symptoms are slowly improving. Additionally, the patient's absolute *CD4+* and *CD8+* counts improved slightly (283 cells/mL and 75 cells/mL, respectively) four months later without further opportunistic infections.

Case Discussion

Bacillary angiomatosis is most commonly reported in patients with HIV/AIDS, although it has also been diagnosed in patients with other immunosuppressive conditions and in immunocompetent patients [1,5]. There have been reported cases of bacillary angiomatosis in patients with chronic lymphocytic leukemia, and chronic myeloblastic leukemia. Bacillary angiomatosis has also been diagnosed in transplant patients and patients undergoing chemotherapy [6-9]. However, to our knowledge, this is the first case reported with underlying idiopathic *CD4+* lymphocytopenia. Our patient meets all three criteria needed to diagnose idiopathic *CD4+* lymphocytopenia: absence of HIV infection, absence of immunosuppressive therapy or a previous diagnosis of an immunodeficient condition, and an absolute *CD4+* T-lymphocyte count of less than 300 cells/mL on two separate occasions at least 6 weeks apart [10,11]. The immunodeficiency caused by idiopathic *CD4+* lymphocytopenia predisposes patients to develop opportunistic infections, such as *Bartonella henselae* [11]. In an idiopathic *CD4+* lymphocytopenia study by Vijayakumar et al., the majority of patients suffered from at least one opportunistic infection, even though none were reported to be with *Bartonella henselae* [11]. The progression of idiopathic *CD4+* lymphocytopenia is highly variable, as absolute *CD4+* counts can become normal over time, stabilize at low levels, or continue to progressively decline. In our case, although the patient's absolute *CD4+* count improved marginally, it remained low for multiple years [12,13]. Long term patient follow-up is important.

The pathogenesis of bacillary angiomatosis includes early hematogenous dissemination of organisms which can result in seeding of the central nervous system [14]. The absence of detection of bartonella on culture and polymerase chain reaction of blood does not preclude this possibility. Bacteremia is significantly underdiagnosed because of the poor sensitivity of these methods for this organism [15]. Furthermore, although serum IgG levels of >/= 1:256 are commonly measured with bacteremia, our patient may have been unable to produce antibodies at detectable levels in the serum owing to his persistently low *CD4+* cell count [16,17]. Immunocompromised patients are also more susceptible to central nervous system complications following infection with *Bartonella henselae*, particularly encephalopathy and aseptic meningitis [18]. There have been reported cases of *Bartonella* species. causing ataxia, memory loss, and tremors in patients without detectable antibodies in the serum [19]. The presence of intrathecal antibodies against *Bartonella henselae* and the improvement in his neurological symptoms on doxycycline seem to argue that neuroinvasion did occur. Even in the absence of frank central nervous system infection by *Bartonella henselae*, it is possible that bacillary angiomatosis resulted in an infection-induced Parkinson disease exacerbation [20].

Conclusion

Bacillary angiomatosis is a rare cutaneous manifestation of *Bartonella henselae* infection that has not previously been reported in a patient with idiopathic *CD4+* lymphocytopenia. Our patient's dermatological findings resolved on appropriate antibiotic therapy and the fact that his neurological symptoms have improved also suggests that the presence of intrathecal antibodies against *Bartonella henselae* reflected concomitant central nervous system infection. His presentation serves as a reminder that bacillary angiomatosis can present in patients with negative HIV status.

Potential conflicts of interest

The authors declare no conflicts of interest.

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