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Successful and Rapid Treatment of Two Patients with Bacillary Angiomatosis with Azithromycin

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Abstract

We report on two homeless, HIV-infected patients with intravenous drug abuse developing a generalized rash composed of angiomatous papules. Based on the clinical manifestations, routine histology and sequencing of bacterial 16S rRNA the diagnosis of bacillary angiomatosis (BA) was established. In addition to treating the underlying HIV infection, the patients received azithromycin leading to complete regression of the cutaneous lesions.

These cases highlight the clinical efficacy of azithromycin in the treatment of bacillary angiomatosis. Compared to the first line treatment of BA with erythromycin, azithromycin has a better tolerability, shows a more favorable drug-drug interaction profile and, most importantly, can be given once daily due to its superior pharmacological properties. Collectively, azithromycin poses an attractive alternative in the treatment of BA, especially in patient populations with low treatment adherence.

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Introduction

Bacillary Angiomatosis (BA) is a rare systemic infection caused by Gram-negative bacteria *Bartonella quintana* and *Bartonella henselae* and occurs most commonly in HIV-infected patients with a marked depletion of $CD4^+$ T cells [1, 2]. Even though every organ system may be involved, most patients present with cutaneous lesions, fever, weight loss and lymph node swelling [3]. Diagnosis is based on distinctive vascular proliferations in microscopic studies as well as the detection of Bartonella spp. using Whartin-Starry staining or molecular techniques such as PCR or sequencing of bacterial 16S rRNA. Currently, treatment recommendations are based primarily on one observational study and a limited number of case reports [4, 5] showing efficacy of both erythromycin and tetracycline. Of note, treatment has to be of sufficient duration (i.e. 8-12 weeks) to prevent relapse regardless of the antimicrobial agent used [6].

Case 1

A 25 year old, heterosexual homeless man with a history of intravenous drug abuse presented with a generalized rash composed of multiple, angiomatous papules [Figure 1a]. The patient was in a bad general state of health showing a BMI of 17 and reported fever, malaise and headache starting three weeks ago. Based on the clinical appearance, the history of intravenous drug abuse and the homelessness we considered the

differential diagnosis of BA underlying an advanced infection with HIV [Table 1]. The histological examination of an angiomatous papule revealed lobular proliferations of blood vessels containing cuboidal endothelial cells indicative of BA [Figure 1b]. This diagnosis was eventually confirmed by the detection of clumps of bacteria using Whartin-Starry staining [Figure 1c]. Sequencing of bacterial 16S rRNA identified *B. quintana* as the causative microbe. As expected, an HIV infection was newly diagnosed showing a severe immunodeficiency with a CD4 cell count of 2 c/mm³ and a high HIV load (log 5.72 cp/ml). A thorough medical check-up including cardiac and lymphnode ultrasound as well as computed tomography of cranium, thorax and abdomen did not show any involvement of other organs.

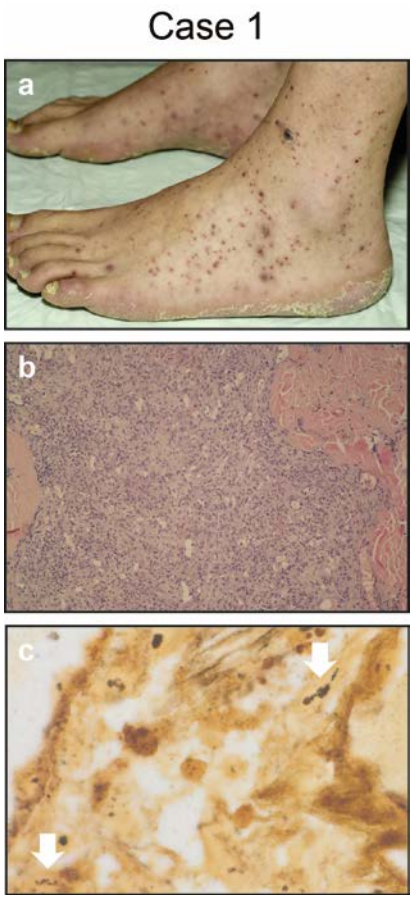

Figure 1: (a) Multiple angiomatous macules and papules on the feet. (b) Routine hematoxylin and eosin staining of one angiomatous papule showing vascular proliferations with dense leukocytic infiltrates. (c) Clumps of bacteria (arrows) in the Whartin-Starry staining.

Based on the diagnosis of an advanced infection with HIV and concomitant BA, combination antiretroviral therapy containing a boosted protease inhibitor as well as an antibiotic prophylaxis with cotrimoxazol/sulfamethoxazol was started. Suspecting a low treatment adherence with erythromycin, requiring the intake of 4 tablets per day and causing significant gastrointestinal side effects we commenced azithromycin 500mg once daily instead. This treatment led to the rapid disappearance of the cutaneous lesions. In total, the patient received azithromycin for five month without suffering any relapse.

Table 1: List of differential diagnoses for bacillary angiomatosis

generalized angiomatous papules	bacillary angiomatosis Kaposi sarcoma Syphilis rickettsial infection

Case 2

A 31 year old, heterosexual homeless man with a known HIV infection due to intravenous drug abuse and a CD4 count of 63 c/mm^3 presented with a generalized, itching rash composed of disseminated angiomatous papules [Figure 2a] but with no other symptoms. He had stopped antiretroviral therapy two years before. Considering his advanced infection with HIV, BA was the primary differential diagnosis [Table 1]. Indeed, histological analysis revealed vascular proliferations showing a dense infiltrate with leukocytes suggestive of BA [Figure 2b]. Even though no bacteria were detectable in Whartin-Starry staining, sequencing of bacterial 16S rRNA of an angiomatous papule identified *B. quintana*, confirming the clinical suspicion of BA. The thorough medical check-up was unremarkable. Consequently, ART containing a boosted protease inhibitor as well as an antibiotic prophylaxis with cotrimoxazol/sulfamethoxazol was reinitiated. Similar to the above patient, we expected a low treatment adherence with erythromycin and, alternatively, started therapy with

azithromycin 500mg once daily. No cutaneous lesions were observed after 3 weeks of treatment and azithromycin was stopped after 3 months.

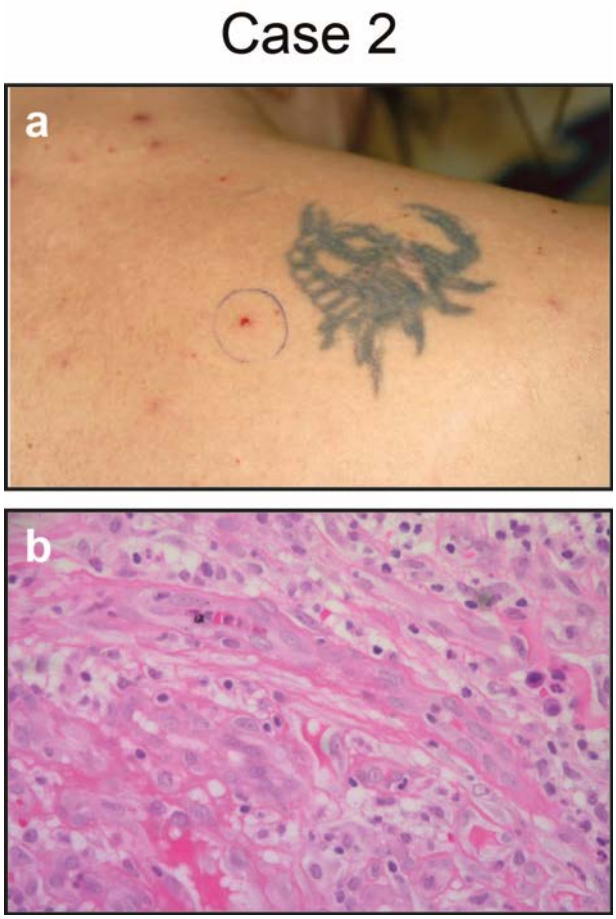

Figure 2: (a) Angioma-like papules on the back. (b) Skin biopsy demonstrating numerous vascular proliferations with cuboidal endothelial cells.

Discussion

Owing to its rare occurrence, treatment of BA has not been systematically studied [5, 6]. Of note, it can be expected that in the near future no systematic studies will be carried out reflecting the general decline of opportunistic infections in HIV-infected patients. Given that the first patient suffering from BA was successfully treated with erythromycin [7], this drug became the first line treatment for this disorder [5, 6] despite its unfavorable side effects, numerous potential drug-drug interactions and, above all, inconvenient dosing (four times a day) [9]. Here, we demonstrate the clinical efficacy and rapid onset of action of oral azithromycin in the treatment of bacillary angiomatosis in two patients with advanced HIV infection, confirming previous observations of clinical efficacy of this drug in the treatment of BA [9, 10]. In contrast to the recommended treatment with erythromycin requiring the intake of four tablets per day, one of the major advantages of oral azithromycin is the once-daily administration due to it is longer half-life [11]. Considering the treatment duration for bacillary angiomatosis of several months, the pill burden could thus be significantly reduced. Especially in patient populations with low treatment adherence such as intravenous drug abusers reducing the pill burden is of utmost importance.

Apart from the superior dosing regimen, azithromycin has a better tolerability than erythromycin or other macrolides causing less gastrointestinal upset and fewer episodes of cardiac QT prolongations [11]. In addition, azithromycin shows a more favorable drug-drug interaction profile than comparable macrolides because it does not induce CYPs. *In vitro*, all macrolides are similarly highly effective in the prevention of Bartonella growth. In some studies Minimal Inhibitory Concentrations (MIC). In some studies MIC for azithromycin and clarithromycin was even lower than for erythromycin [3, 5]. Finally, azithromycin accumulates more effectively in phagocytes than erythromycin and other macrolides, resulting in a higher concentration of the antimicrobial molecule at infectious sites, including in the skin [11, 12]. Taken together, azithromycin proves to be efficacious both *in vitro* [3, 5] and *in vivo* [9, 10] against the causative agent of BA.

In conclusion, azithromycin represents a suitable alternative to the current standard of care of BA owing to its superior pharmacological properties [11]. Ideally, this assumption will be confirmed in a randomized controlled clinical trial.

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