HIV AND BURULI ULCER
AN EXHAUSTIVE LITERATURE REVIEW

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1 INTRO-DUCTION

During the last few years, the interest in HIV-Buruli ulcer (BU) interaction has increased among Buruli ulcer experts. Some studies have been published on the subject, however most of them are case reports. The majority of published studies are compatible with 1) the hypothesis that HIV increases the risk of developing BU and 2) the hypothesis that HIV (and implicitly HIV immunosuppression) is associated with more severe BU disease. A few published studies contradict these hypotheses; some suggest that other independent factors might be associated with severe BU.

The primary aim of this study is to examine the literature on how HIV affects BU in terms of clinical and immunological manifestations. Others aspects of the interaction will be described as well. The secondary purpose is to elaborate research questions and define further research required to answer these remaining questions.

2 METHODS

References where both HIV and BU appear are very scarce. The only productive databases that were used for this review were Pubmed, Google Scholar and Google. The literature review was performed until the 3 of March 2015. The key words used for database search were: HIV, AIDS, Buruli Ulcer, Mycobacterium ulcerans, VIH, SIDA and ulcère de Buruli. The different articles reviewed were screened for references on the topic of interest and if relevant, they were included in the review.

All the references which included BU cases with HIV tests performed were selected. The references were listed in a table and then grouped according to the subject of interest.

3 RESULT

HIV is a risk factor for BU

In several countries in Sub-Saharan Africa, 6 studies (2 case-control [1,2] and 4 cohorts of BU patients [3-6]) were performed with systematic HIV testing of BU patients; one included only children [5]. Two additional references describe smaller BU cohorts with half of the BU population tested for HIV [7,8], one of them included only BU with bone involvement [8]. In all these studies the prevalence rate of HIV among patients with BU is higher than the controls or than a referenced population (national or regional prevalence rate or age and sex reference group prevalence rate).

One randomized controlled trial on BU treatment shows a lower prevalence rate of HIV among BU cases [9] than the national adult HIV prevalence. In this study more than 50% of the study population was less than 12 years old, a population less affected by HIV infection.

One Australian cohort of 180 BU patients, not systematically tested for HIV, showed no HIV positive cases (10). Australian HIV prevalence in this region in particular and in Australia in general, is particularly low.

4 RESULT

HIV (induced immune-suppression) is worsening Buruli Ulcer clinical presentation

HIV is associated with severe BU lesions in a large cohort study on 1511 patients conducted in Benin (OR 2·77, 95% CI 1·32–6·33; p=0·006) [3]. In another cohort study HIV positive patients presented with significantly more multifocal BU lesions (24% vs 11%; P = .004) [4]. One study considering only BU with bone involvement in Benin [8] and one considering only multifocal BU in Ivory Coast [11] show a particularly high HIV prevalence rate (36% and 32% respectively).

There is one retrospective analysis of 92 HIV positive BU patients with CD4 cell counts available in Cameroon. BU lesion size was inversely associated with a CD4 cell count < 500 cell/mm3 (β-coeff., −0.50; P = .015; 95% CI −0.91–0.10). Time to BU wound closure was more than doubled when CD4 cell counts were below 500 cell/mm3 (HR, 2.39; p= 0.001; 95% CI, 1.44–3.98) [4].
Ten BU cases in HIV positive patients with either CD4 counts available or an AIDS defining illness are reported. In 9 case reports, severe BU lesions correlate with low CD4 cell count or AIDS [2,4,12-18]. One case of BU, described as typical BU with a good evolution, is reported in an HIV positive woman with a CD4 cell count of 500 cell/mm3 (not considered as significantly immunosuppressed).
There was one case of severe BU in a HIV positive patient without a CD4 cell count available and the patient died [19] and one case of severe facial BU with documented HIV without a CD4 cell count available [20].
Several cases of non-severe typical BU with good evolution are reported in HIV positive patients. No information is given regarding their CD4 cell counts [7,21].

Severe BU cases with some very extensive lesions are reported in 8 HIV negative children [22–28]. Co-morbidities such as malnutrition, sickle cell trait, anemia and malaria are reported in some cases [25,27].

5 RESULT

Does HIV increase the risk of M.Ulcerans hematogenous bone infection?

References show contradictory results. In one study focusing on bone involvement, with all cases proven as M .ulcerans bone infection by PCR, HIV is considered a risk factor, in particular, for further hematogenous bone dissemination [8]. However, in contrast, in BU population studies the proportion of patients with bone involvement is generally less frequent among HIV-positive than among HIV-negative patients [2,3,29]

High mortality rate in HIV-BU co-infected patients

In HIV negative patients, mortality associated with Buruli ulcer is rare. In HIV-BU co-infected patients the mortality rate is much higher. Many studies / case reports relate death among co-infected patients, sometimes despite anti-retroviral treatment and relatively high CD4 cell counts. [6,18,19,30–32]. In a BU cohort in Cameroon including 459 patients 11% of HIV-BU co-infected patients died compared to 1% of BU patients with a documented HIV negative test (p<0.001). The median CD4 cell count among the 8 deceased patients was 228.5 cell/mm3 (IQR, 98–378). None was under antiretroviral therapy (ART).The median duration of time to death was 41.5 days (IQR, 16.5–56.5). [4]

6 DISCUS-SION

There are potential biases in this review; bias inherently linked to the studies such as HIV testing bias and publication bias.
There are confounders such the use of traditional herbs, which might be frequently used in HIV positive patients and could worsen BU, which in most cases is not taken into account.
Moreover it appears that in some cases HIV positive patients with severe BU have a long BU evolution history before entering medical care, which could be related to the stigmatization of both infections (HIV and BU). This can also be a confounder for severe lesions observed among some HIV positive patients [20].
However, in the Cameroon study, BU evolution history was not a significant factor associated with increased BU lesion size in the multivariate analysis of HIV positive patients. The use of traditional medicine was the only other factor, in addition to low CD4 cell count, significantly associated with a larger BU lesion size [4].

7 CONCLU-SION

HIV infection likely increases the risk of developing BU and results in more severe clinical BU disease. HIV immune suppression appears to be an important factor in cases of severe BU, particularly among adults.
The magnitude of HIV's impact on BU varies from one setting to another, depending on local HIV and BU prevalence. It also depends on the relative age and sex related HIV prevalence.
In settings where HIV and BU prevalence are high, the management of co-infected patients represents significant management challenges to health workers. **Further studies are needed** to provide scientific evidence that may lead to improvements in the clinical care of co-infected patients and to a strengthening of WHO guidance on HIV-BU co-infection.

1. Raghunathan PL, Whitney EA, Asamoa K, Stienstra Y, Taylor TH, Jr., et al. (2005) Risk factors for Buruli ulcer disease (Mycobacterium ulcerans Infection): results from a case-control study in Ghana. Clin Infect Dis 40: 1445-1453.
2. Johnson RC, Nackers F, Glynn JR, de Biurrun Bakedano E, Zinsou C, et al. (2008) Association of HIV infection and Mycobacterium ulcerans disease in Benin. AIDS 22: 901-903.
3. Vincent QB AM, Marsollier L CA (2014) HIV infection and Buruli ulcer in Africa. The Lancet 14: 796-797.
4. Christinet V (2014) Impact of Human Immunodeficiency Virus on the Severity of Buruli Ulcer Disease: Results of a Retrospective Study in Cameroon. Open Forum Infectious diseases 1: 1-9.
5. Aissan (2000) Contribution à l'étude de certains aspects immunologiques de l'UB au Bénin (Medicine). Cotonou. Universtity Nation Bénin. 87pp p.
6. Darie H, Le Guyadec T, Touze JE (1993) [Epidemiological and clinical aspects of Buruli ulcer in Ivory Coast. 124 recent cases]. Bull Soc Pathol Exot 86: 272-276.
7. Asiedu K, Etuaful S (1998) Socioeconomic implications of Buruli ulcer in Ghana: a three-year review. Am J Trop Med Hyg 59: 1015-1022.
8. Portaels F ZC, Aguiar J, Debacker M, de Biurrun E, Guédénon A, Josse R, Lagarrigue V, Silva MT, Steunou C., WM M (2003) Les atteintes osseuses dans l'ulcère de Buruli : A propos de 73 cas. Bull Séanc Acad R Sci Outre-Mer 49: 161-190.
9. Nienhuis WA, Stienstra Y, Thompson WA, Awuah PC, Abass KM, et al. (2010) Antimicrobial treatment for early, limited Mycobacterium ulcerans infection: a randomised controlled trial. Lancet 375: 664-672.
10. Boyd SC, Athan E, Friedman ND, Hughes A, Walton A, et al. (2012) Epidemiology, clinical features and diagnosis of Mycobacterium ulcerans in an Australian population. Med J Aust 196: 341-344.
11. Ouattara D, Meningaud JP, Saliba F (2002) [Multifocal forms of Buruli ulcer: clinical aspects and management difficulties in 11 cases]. Bull Soc Pathol Exot 95: 287-291.
12. Bahebeck J, Bedimo R, Eyenga V, Kouamfack C, Kingue T, et al. (2004) The management of musculoskeletal infection in HIV carriers. Acta Orthop Belg 70: 355-360.
13. Johnson RC, Ifebe D, Hans-Moevi A, Kestens L, Houessou R, et al. (2002) Disseminated Mycobacterium ulcerans disease in an HIV-positive patient: a case study. AIDS 16: 1704-1705.
14. Wanda F, Nkemenang P, Ehounou G, Tchaton M, Comte E, et al. (2014) Clinical features and management of a severe paradoxical reaction associated with combined treatment of Buruli ulcer and HIV co-infection. BMC Infect Dis 14: 423.
15. Komenan K, Elidje EJ, Ildevert GP, Yao KI, Kanga K, et al. (2013) Multifocal Buruli Ulcer Associated with Secondary Infection in HIV Positive Patient. Case Rep Med 2013: 348628.
16. Toll A, Gallardo F, Ferran M, Gilaberte M, Iglesias M, et al. (2005) Aggressive multifocal Buruli ulcer with associated osteomyelitis in an HIV-positive patient. Clin Exp Dermatol 30: 649-651.
17. Roussel M TN, Prevot G, Sainte-Marie D, Maubert B, Marcellier L, Pradinaud R, Couppié P (2004) RÉMISSION CLINIQUE ET MICROBIOLOGIQUE D'UNE INFECTION A MYCOBACTERIUM ULCERANS (ULCÈRE DE BURULI) CHEZ UNE PATIENTE VIH+ APRÈS 5 MOIS DE TRAITEMENT PAR L'ASSOCIATION RIFABUTINE-CLARITHROMYCINE WHO Buruli Conference.
18. Bafende AE, Lukanu NP, Numbi AN (2002) Buruli ulcer in an AIDS patient. S Afr Med J 92: 437.
19. Kibadi K, Colebunders R, Muyembe-Tamfum JJ, Meyers WM, Portaels F (2010) Buruli ulcer lesions in HIV-positive patient. Emerg Infect Dis 16: 738-739.
20. Kouame K KK, Ecra E, Kouakou H N., Kaloga K, Ahogo K (2005) Prise en charge médico-chirurgicale des atteintes céphaliques de l'ulcère de Buruli. Bull Soc Pathol Exot 98: 55.
21. Allen S (1992) Buruli ulcer and HIV infection. Int J Dermatol 31: 744-745.
22. Bessis D, Kempf M, Marsollier L (2014) Mycobacterium ulcerans Disease (Buruli ulcer) in Mali: A New Potential African Endemic Country. Acta Derm Venereol.
23. Sarfo FS, Thompson W, Phillips RO, Paintsil A, Abass MK, et al. (2014) A severe case of Buruli ulcer disease with pleural effusions. PLoS Negl Trop Dis 8: e2868.
24. Ruf MT, Sopoh GE, Brun LV, Dossou AD, Barogui YT, et al. (2011) Histopathological changes and clinical responses of Buruli ulcer plaque lesions during chemotherapy: a role for surgical removal of necrotic tissue? PLoS Negl Trop Dis 5: e1334.
25. Sopoh GE, Dossou AD, Brun LV, Barogui YT, Houezo JG, et al. (2010) Severe multifocal form of buruli ulcer after streptomycin and rifampin treatment: comments on possible dissemination mechanisms. Am J Trop Med Hyg 83: 307-313.
26. Ecra E (2001) ULCERE DE BURULI : À PROPOS DE DEUX CAS THORACO-ABDOMINAUX ASSOCIÉS À UNE PLEURÉSIE. Médecine d'Afrique Noire 48: 213-216.
27. Pszolla N, Sarkar MR, Strecker W, Kern P, Kinzl L, et al. (2003) Buruli ulcer: a systemic disease. Clin Infect Dis 37: e78-82.
28. Meyers WM, Tignokpa N, Priuli GB, Portaels F (1996) Mycobacterium ulcerans infection (Buruli ulcer): first reported patients in Togo. Br J Dermatol 134: 1116-1121.
29. Reith C PS (2014) Ostéites à Mycobacterium ulcerans au Cameroun [Medical Master Thesis].
30. Bayonne Manou L S. PF, Eddyani M., Book A U., Vandelannoote k., de Jong BC (2013) L'infection à Mycobacterium ulcerans (ulcère de Buruli) au Gabon de 2005 à 2011. Médecine et Santé Tropicales 23: 450-457.
31. portaels F AJ, Debacker M, Johnson C, Meyers WM (2008) Les atteintes osseuses dans l'ulcère de Buruli: une revue de 186 cas traités à Zagnanado (Bénin). Bull de l'ALLF 23: 48-50.

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