MYCOBACTERIUM ULCERANS DISEASE (BURULI ULCER) IN A RURAL HOSPITAL IN BAS-CONGO, DEMOCRATIC REPUBLIC OF CONGO, 2002–2004

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Abstract. Buruli ulcer (BU), which is caused by *Mycobacterium ulcerans*, is an important disabling skin disease. Its prevalence is highest in west and central Africa. We report an apparent resurgence of BU in the Bas-Congo Province, Democratic Republic of Congo. During a 28-month period in 2002–2004, the rural hospital of the Institut Médical Evangélique at Kimpese admitted 51 patients suspected of having BU. Bacteriologic, molecular biologic, and histopathologic studies confirmed BU in 36 of these patients. Extensive clinical data, treatment outcomes, and socioeconomic correlations are summarized. Osteomyelitis was an important complication. A multidisciplinary approach to BU control in the Bas-Congo is proposed, aimed primarily at active case detection.

INTRODUCTION

Buruli ulcer (BU) is a severe disfiguring and disabling infectious disease caused by *Mycobacterium ulcerans*, a bacterium related to those causing leprosy and tuberculosis. The disease has emerged dramatically over the past decade particularly in west Africa, and has been detected or suspected in at least 31 countries.[1,2] The first case, which was reported in 1950 in the Democratic Republic of Congo (DRC), was an American boy living in the Kwilu region.[3]

Information on BU in the DRC was summarized by Janssens in 1972[4] and by Meyers and others in 1974.[5] The District of Cataractes in Bas-Congo (Lower Congo) Province is one of the main regions of the DRC where BU has been reported.[5–10] Bas-Congo is one of the 11 provinces of the DRC, is situated in the southwestern part of the country, and has a population of 2,835,000. This province has 27 health zones and five districts (Figure 1): Matadi (the main town), Boma (the second largest town), Bas-Fleuve, Cataractes, and Lukaya.

The population of the DRC was approximately 50 million in 2002 and reached 60 million in 2005 (National Institute of Statistics). Seventy percent of the people live in rural areas, 57% are ≤ 19 years old, and 39% are 20–50 years old. Between 1972 and 1990 the national health budget decreased from 2.4% to 0.7% with one physician per 22,637 inhabitants and one nurse per 1,714.

The Institut Médical Evangélique (IME)/Kimpese serves an area with approximately 150,000 inhabitants, has 400 beds, and receives most of the hospitalized BU patients in the province. This hospital is 220 km southwest of Kinshasa in Songololo Territory, the main known focus of BU in the DRC.[5–12] Although many observations have been reported from IME/Kimpese,[5–10] no recent data have been published on patients with a laboratory-confirmed diagnosis of BU according to the World Health Organization (WHO) criteria.[13] This study reviews the experience of IME/Kimpese in the management of hospitalized laboratory-confirmed BU patients from May 2002 to August 2004.

MATERIAL AND METHODS

We studied 51 consecutive suspected BU patients admitted to the surgical service of IME/Kimpese in the Province of Bas-Congo from May 2002 to August 2004. Age, sex, address, date of onset, date of diagnosis, clinical features, hospital stay, type of management, and evolution of the disease were recorded. Recognized clinico-epidemiologic features were used to suspect lesions as BU.[1,13] As required by the Medical Committee of IME/Kimpese all patients, or their responsible relative or guardian, gave informed consent for all diagnostic and treatment procedures.

Specimens of exudates and tissues from all 51 patients were obtained and evaluated according to WHO recommendations.[13] The initial direct smear examinations for acid-fast bacilli and histopathologic analyses were made at the IME/Kimpese laboratory. Other specimens from the same patient were sent in a transport medium[13] to the Mycobacteriology Unit of the Institute of Tropical Medicine (ITM) in Antwerp, Belgium, where Ziehl-Neelsen (ZN) staining, *in vitro* culture, and an IS*2404* polymerase chain reaction (PCR) were performed.[13] Formalin-fixed tissues were sent to the Department of Infectious and Parasitic Diseases Pathology of the Armed Forces Institute of Pathology in Washington DC, for confirmation of the histopathologic diagnosis. Data were recorded using Excel (Microsoft Corporation, Redmond, WA) and analyzed with Epi-Info (Centers for Diseases Control and Prevention, Atlanta, GA) and SPSS version 9.0 for Windows (SPSS Inc., Chicago, IL).

RESULTS AND DISCUSSION

Among 51 patients clinically suspected to have BU, 36 (70.5%) had laboratory-proven *M. ulcerans* disease. They had positive results for at least one of the laboratory tests used, i.e.: ZN staining, culture, PCR or histopathologic diagnosis. Twenty-six of 36 had at least two positive tests results and 10 of 36 had only one positive test result. The distribution of the positive test results for diagnosis of BU was ZN staining (61.1%), PCR (75%), histopathologic diagnosis (75%), and culture (2.8%). Except for culture results, this distribution compares favorably with previously published data.[13] Several explanations for the low percentage of positive primary cul-
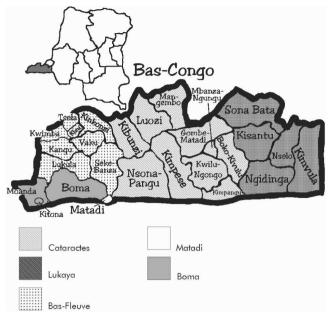
FIGURE 1. Map of Bas-Congo province with 27 Health Zones, among which are three main regions endemic for Buruli ulcer: the zones of Kimpese, Nsona-Mpangu, and Kwilu-Ngongo.

tures have been discussed by several investigators.[13–15] Secondary infections of skin ulcers in 52.8% of our patients, difficulties with sampling, and transportation delay (> 2 months) to the ITM in Belgium were the most likely contributing factors. Ideally, specimens should be processed on the day of collection to obtain maximum positivity rates for primary cultures.[1] Some investigators have obtained > 60% positivity rates for primary cultures after storage of tissue specimens in a semisolid transport medium[13] kept at 4°C for one week before processing.[16]

Fifteen patients (29.4%) had negative results. Among them, three had negative results in the four tests and 12 were partially tested. Five patients had another diagnosis (one with malignant non-Hodgkin's lymphoma, one with Kaposi's sarcoma, and three with non-specific chronic inflammation and necrosis).

The age distribution of the BU patients during this period showed that 16 (44.4%) of 36 patients were less than 15 years of age, 36.1% were 16–45 years of age, and 19.4% were more than 45 years of age. The median age was 17 years (age range = 3 months to 67 years). This is similar to previous studies that reported rates of 48.0% to 64.0% of patients less than 15 years of age in the same area.[10,17] A study of 151 BU patients treated and followed-up between 1998 and 2000 by the health center of Lalo (Couffo Department, Benin) showed similar results: 46.4% less than 15 years of age, 40.4% between 15 and 49 years of age, and 13.3% more than 49 years of age.[17] However, the proportion of 70% of patients less than 15 years of age found in other disease-endemic countries is higher than in the present study.[1] Debacker and others in a study of 1630 BU patients in Benin reported a median age of 15 years and an age range of 2 months to 83 years.[18] This is also similar to our observations.

From May 2002 to August 2004, three times more males (n = 27) than females (n = 9) were diagnosed (75% versus 25%), which is consistent with a previous report from the

same geographic area.[12] However, other reports show an equal proportion of males and females, both in the area of this study[10] and other areas.[1,11,18] It is likely that socioeconomic factors in our region result in males seeking hospital care more often than females.

Among our BU patients, 91.7% came from the Cataractes District, 5.6% from the Bas-Fleuve District, and 2.8% from the Matadi District (Table 1). No patients were diagnosed in the Boma and Lukaya Districts. Most (58.3%) BU patients were Congolese and 41.7% (15 of 36) were Angolan (Table 1). Bas-Congo Province borders northern Angola. The possibility of infection in Angola is considered low, although cases of BU have been reported in Angola.[19,20] Meyers and others reported BU in the Lower Congo in newly arrived patients from Angola beginning in 1965.[5] In our report, however, most of the Angolan BU patients had lived in the DRC for several years, and some young Angolan patients born in Bas-Congo had never visited Angola. Among Angolans living in refugee camps, we believe most patients were either infected while living near Songololo, the usual point of entrance for Angolan refugees, or in refugee camps located in this region that is highly endemic for BU. Despite the availability of a safe water supply, the refugees frequent surrounding rivers and wetlands for domestic water (laundry, bathing and agricultural activities).

Recently, an environmental study showed that the Kimu River near the Angolan refugee camp of Nkondo in Kimpese was positive for *M. ulcerans* by IS*2404* PCR.[21] Songololo Territory, which is where our hospital is located, has remained the primary source of BU patients for more than 40 years.[5–7,11] Most (94.4%) patients had ulcerative skin lesions and two (5.6%) had non-ulcerative *M. ulcerans* disease (one edema and one plaque). There was superinfection of skin ulcers in 52.8% of the BU patients. Disability was noted in 25% on admission.

Clinical forms were distributed as follows: mixed forms in 61.1%, single ulcerative lesions in 33.3%, plaque in 2.8%, and edema in 2.8%. Ulcers were present in all mixed forms. Bone involvement was suspected in 36.1% of the patients. Osteomyelitis caused by *M. ulcerans* was confirmed in 6 (16.70%) of these patients. Two patients had gram-positive and gram-negative bacterial infections and one had a fungal infection of the bone. These findings are consistent with the rate reported in BU patients with osteomyelitis (14%) in Benin.[17,22] Table 2 shows the location of the lesions and the total distribution of lesions including those that had multiple areas involved. The lower limbs were the most frequently involved (63.9%), followed by the upper limbs (44.4%), thorax (5.5%), back

TABLE 1
Origin of Buruli ulcer patients, 2002–2004, Democratic Republic of Congo (Bas-Congo)

District	Health zone	No.*	%	Total % per district
Bas-Fleuve	Sekebanza	1	2.8	5.6
	Tshela	1	2.8	
Cataractes	Kimpese	15 (9)	41.7	
	Kwilu-Ngongo	7 (1)	19.4	91.7
	Nsona-Mpangu	11 (5)	30.5	
Matadi	Matadi	1	2.8	2.8
Total		36 (15)	100	100

* Values in parentheses are no. of Angolan patients.

TABLE 2
Site of lesions in Buruli ulcer patients

Site of lesions	N = 36 no. (%)
Back	2 (5.5)
Head	1 (2.8)
Thorax	1 (2.8)
Upper limbs	9 (25)
Lower limbs	14 (38.9)
Lower and upper limbs	7 (19.4)
Lower limb and head	1 (2.8)
Lower limb and thorax	1 (2.8)
Lower limbs (total)	23 (63.9)
Upper limbs (total)	16 (44.4)

(5.5%), and head (5.5%). This is consistent with another report on the distribution of lesions.[17]

During the 28 months from May 2002 to August 2004, the admission rate at the IME was 15.4 patients/year. Between 1960 and 1970, 130 patients were treated at IME (13/year). A study program for *M. ulcerans* infection that included a special treatment ward was established in late 1970 at the same hospital, and several rural dispensaries and outlying hospitals were contacted. This resulted in the treatment of 39 patients in 1971.[5] The admission rate was 4.5 patients/year from 1989 to 1999 and 31 patients/year from 2000 to 2001.[10] The lowest rates of admission were recorded from 1989 to 1999. This is probably due to a loss of specialized personnel in the hospital during this period. The highest rate of admission, which was recorded from 2000 to 2001, was most likely attributable to the high proportion of Angolan refugees referred by new health centers in refugee camps, which represented 50% of all BU patients.[12] Since most reports are based on passive presentation of patients to the hospital, these numbers represent gross underreporting.[1] In 1974, Meyers and others reported that the patients presenting at IME/Kimpese with BU represented only a small percentage of the total number afflicted by this disease.[5] In July 2002, a joint research team of IME/Kimpese and the ITM/Antwerp reported 34 suspected cases during two half days of active case finding in Songololo Territory (Polman K and Phanzu MD, unpublished data). In October 2003, 21 suspected BU patients were reported after one day of active survey within 5 km of Nsona-Mpangu Hospital where only one patient was hospitalized (Phanzu DM and others, unpublished data).

The median delay in seeking medical care was 60 days with a minimum of 7 days and a maximum of 840 days (Phanzu DM and others, unpublished data). Overall median delay in Benin from 1989 to 2001 decreased from approximately four months to one month.[17] In this country, the introduction of a BU program of the Directorate General for Development Cooperation (DGDC, Belgium) was an important factor in the marked reductions in patient delay. Moreover, in 2000, after promotional sessions on BU organized by the DGDC and the National BU Program in the Zou, Oueme, and Atlantique Departments, patients reported earlier than in 1999 to the health center at Zagnanado in the Zou Region.[17]

We expect the admission rate to increase at the IME/Kimpese Hospital with the inauguration of the Program National de Lutte contre l'Ulcère de Buruli (PNLUB), which was started by the Ministry of Health of the DRC in 2002. In May 2003, the first conference on the control of BU was organized in Bas-Congo, the main disease-endemic region nearest the national capital of Kinshasa. The first national workshop took place in September 2004. The PNLUB seeks collaboration with national or international organizations to strengthen control measures and treatment programs.

In this study, 5 patients presented spontaneously and 31 (86.1%) were referred by government health centers or other health professionals. Only 45.2% (14 of 31) were referred with a suspicion of BU, among whom 12 were referred by a health center where a well-trained doctor well-informed about BU was working. At the health center in Zagnanado, Benin, 68.3% of the patients were referred by a previously treated patient, 22.1% by a family member acquainted with the health center, 5.9% by village outreach activities of the health center, and only 3.7% by health professionals.[17] The strikingly different referral method compared with those at Kimpese is most likely related to the high number (> 4,000) of successfully treated patients in Benin since 1989.[17] In Zagnanado, Benin, referral of patients to a BU treatment center depends largely on word-of-mouth information from former BU patients. We are hopeful that similar results will develop at IME/Kimpese.

Among our patients 61.1% were new cases (n = 22) and 38.9% were relapses (n = 14). Among relapsed cases, eight were previously treated by surgery at IME/Kimpese, three at health centers, and three by traditional practitioners. Rates of recurrence for any of these treatment situations are unknown. A study at the health center of Lalo (Couffo Department, Benin) reported a relapse rate of 9.3%, whereas the recurrence rate in Zagnanado (Zou department, Benin) of patients treated after up to 7 years follow-up was 6.1% (*Ahodehou Gandji FU, 2000. Contribution à l'Étude des Récidives d'Ulcère de Buruli à Lalo dans le Département du Couffo. Thèse de Doctorat en Médecine. Faculté des Sciences de la Santé, Cotonou, Bénin No. 872*).[23] The low recurrence rate in Zagnanado is partly due to the early presentation of patients, easy access to treatment, educational sessions conducted by the health center in village, and the quality of surgical treatment.[23] Our patients must travel long distances to reach the BU treatment center of IME/Kimpese. Physical impairments were present in 37% of our patients with obvious long-term social and economic impacts. This is high compared with other reports, indicating that patients with healed lesions had inappropriate management of their physical impairments.[13]

The observations in this study demonstrate the importance of appropriate management of the disease. Our hope is that treatment can be further improved with better resources that are now available. The fact that 94.4% of our patients had an ulcerative form sometimes associated with other clinical forms suggests that our BU patients arrived at an advanced stage of illness, usually with physical impairments or other serious complications such as sepsis, dissemination, and bone involvement. Consequently, these patients had long hospital stays (median = 102 days) and an unusually high mortality rate of 19.4%. Meyers and others noted that the reasons for many BU patients delaying to seek medical assistance were obviously complex, but cultural, economic, and transportation factors were especially important.[5] Thus, this complexity requires a multidisciplinary approach that involves education of the population, training healthcare workers, and managing cases adequately to shorten hospitalization time and stimulate patient initiative.[1,17] Such a multidisciplinary approach will be

possible in Kimpese through a Specific Targeted Research Project sponsored by the European Commission entitled "Buruli ulcer: multidisciplinary research for improvement of control in Africa."

In conclusion, the Province of Bas-Congo (Lower Congo) is a region with endemic BU, particularly in the Cataractes District. Prevalence and incidence are high but surveys are urgently needed. The economic and social impacts of BU are believed to be serious but have never been evaluated. One goal of this report was to establish the need of a Program for BU at IME/Kimpese to serve as a pilot project for the management of this disease. A multidisciplinary approach is being implemented to improve BU control. This includes early detection by active case finding and early treatment to prevent severe handicaps, relapses, unusually high death rates, and exorbitant costs.

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