RESEARCH PAPER

Herpes zoster: clinical, therapeutic, and outcome aspects among HIV-infected patients in Yaoundé, Cameroon

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Abstract

Introduction: Addressing the scarcity of data on therapeutic and evolutional aspects of herpes zoster in Cameroon, the present study aims to describe the clinical, therapeutic and evolutional profiles of herpes zoster among HIV-infected patients in Yaoundé, Cameroon.

Material and methods: From March to May 2015, we conducted a descriptive cohort study at the day-care unit of the Yaoundé Central Hospital, Cameroon. All HIV infected patients visiting the unit, diagnosed with herpes zoster during dermatology consultations, and volunteering to participate in the study were included. They were subsequently followed up at 15 days, at one, and two months.

Results: Overall, 38 patients (78.9% females) were enrolled. The mean age was 39.7 ± 12.6 years. Herpes zoster enabled the diagnosis of HIV infection in 60.5% of cases. The median CD4 count equaled 186 (interquartile range, 70-316) cells/mm^3. At presentation, 26 patients (68.4%) were presented with acute dermatologic lesions, predominantly localized on the chest (34%). All patients complained of pain at the initial visit. Acyclovir was prescribed to twenty patients (52.6%) for 10 days. A decline in the proportion and intensity of pain was noticed over time, though there was no significant difference between those on acyclovir and their acyclovir-naïve counterparts ($p > 0.05$).

Conclusions: This study confirms herpes zoster as a mode of revelation of HIV infection in our context, though its prevalence may be low. Herpes zoster-related pain may be of moderate to severe intensity; therefore, it requires more attention when managing affected patients.

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Introduction

Herpes zoster is a frequent infectious pathology, occurring after reactivation of the varicella-herpes zoster virus (VZV) at the level of the sensitive pre-synaptic ganglion [1]. The VZV will cause varicella during the primary infection, and herpes zoster in case of recurrences [2].

Varicella-herpes zoster virus reactivation may be driven by advanced age and/or immunodeficiency (notably in case of HIV infection, Hodgkin's disease, lymphoma, or an immunosuppressant treatment). Herpes zoster presents as an unilateral vesicular eruption, often limited to a single dermatome [3]. The eruption is usually preceded or accompanied by intense pain, described as acute zoster neuralgia (AZN) [4]. This pain can become severe and prolonged, and it can significantly alter patients' health-related quality of life [5, 6].

The natural history of herpes zoster is usually simple, the disease is ending without leaving any deleterious sequelae. However, the HIV pandemic has completely modified the epidemiology and clinical presentation of herpes zoster. There is sufficient evidence pointing herpes zoster as a reliable predictor of HIV infection, with positive predictive values ranging from 80 to 100% [7]. Indeed, the incidence and severity of herpes zoster negatively correlate with decreased immunodeficiency. It has been reported that an incidence of 31.2 per 1,000 persons per year corresponds to a CD4 count between 200 and 499 cells/mm^3, and an incidence of 97.5 per 1,000 persons per year, a CD4 count < 200 cells/mm^3 [8].

Herpes zoster management is based on initiation of a specific antiviral treatment within 72 hours after occurrence of the first vesicular eruption. Early initiation of the antiviral treatment aims to limit viral replication and the inflammation process, in order to accelerate recovery, decrease AZN intensity, and prevent the development of long-term complications such as post-zoster neuralgia (PZN) [7, 9]. Using acyclovir as the antiviral treatment, Abdelmalek *et al.* observed a 50% reduction in the incidence of PZN among their 92 patients, after 42 days of therapy [1]. The same authors suggested that the antiviral treatment should be strongly recommended when treating HIV-infected patients suffering from herpes zoster [1].

In Cameroon specifically, Njamnshi *et al.* found that neuralgia was the most frequent complication occurring in the course of the herpes zoster infection, more often reported among HIV-infected patients [7]. Nonetheless, there is lack of Cameroonian data on treatment aspects and evolution of herpes zoster. Therefore, the present study was aiming to describe the treatment aspects of herpes zoster management and its related clinical outcomes, especially PZN occurrence among HIV-infected patients living in Yaoundé, Cameroon.

Material and methods

Study design, setting, and participants

From March to May 2015, we conducted a prospective cohort study at the day-care unit of the Yaoundé Central Hospital, Cameroon. This unit is one of the most important HIV clinics in the country, with an active cohort of about 40,000 patients being regularly followed up. It comprises a dermatology service and uses a computerized database to manage patients' medical records.

Participants were HIV-positive patients regularly followed up at the study site, diagnosed with herpes zoster after the dermatology consultation, and who volunteered to participate in the study. These patients were to be followed up during two months. Patients with an altered general state or who refused to participate in the study were not included. Additionally, patients who did not attend their follow-up visits were excluded from further analyses.

Data collection

Patients were recruited during dermatology consultations. Those who fulfilled our inclusion criteria were explained all aspects and procedures regarding the study. Once they volunteered to be included, they were administered a standardized and pre-tested questionnaire. This comprised socio-demographic characteristics (age, sex, profession, marital status, and educational level), medical history (duration of HIV infection, last CD4 count level, duration of symptoms, clinical presentation [type and localization of lesions], presence and intensity of pain [AZN]), therapeutic aspects (antiviral treatment used, duration between onset of symptoms and initiation of antiviral treatment, duration of antiviral treatment, adherence to treatment, other treatments used [analgesics, antibiotics, antiseptics, soaps]).

The patient was given subsequent follow-up visits at 15 days, one, and two months. At each visit, the patient was reassessed and examined. Outcome data were collected, among which the aspects of cutaneous lesions, presence and type of complications (especially the PZN) were included. Pain intensity, either for AZN or PZN, was assessed using the visual and analogic scale; the score was grouped into three categories: mild (between 0 and 4), moderate (5-7), and severe (≥ 8).

Statistical methods

Data were coded and entered using Microsoft Excel 2007, and analyzed with Epi Info version 3.5.4 (CDC Atlanta, USA) and R version 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria). Results are presented as count (percentage) for qualitative variables, and mean ± standard deviation or median (interquartile range) where appropriate, for quantitative variables. The Kaplan-Meier method served to represent PZN evolution over time. The Log-rank test was used to undertake comparisons between those who received the antiviral treatment and those who did not. The Cox regression model was used to seek for factors influencing the occurrence of PZN; hazard ratios (HR) with their 95% confidence intervals (CI) were calculated accordingly. The level of statistical significance was set at $p < 0.05$.

Table 1. Sociodemographic characteristics of the study population

Educational level	Frequency	Percentage (%)
Never gone to school	1	2.6
Primary school	13	34.2
Secondary school	18	47.4
University/College	6	15.8
Profession	**Frequency**	**Percentage (%)**
Housewife	15	39.5
Trader	6	15.8
Farmer	6	15.8
Civil servant	5	13.2
Pupil/student	4	10.5
Unemployed	2	5.3
Marital status		
Single	17	44.7
Married	12	31.6
Widower	4	10.5
Concubinage/cohabitation	3	7.9
Divorced	2	5.3

Ethical considerations

This study was granted an ethical clearance by the Ethical Review Board of the Faculty of Medicine and Biomedical Sciences, University of Yaoundé I, Cameroon. Additionally, administrative authorizations were obtained from the directory of the Yaoundé Central Hospital. All aspects and procedures of the study were fully explained to each potential participant, who was then included only after he/she has voluntarily agreed to take part, and signed an informed consent form accordingly. The participant was free to leave the study at any moment without any prejudice. All information collected was kept confidential.

Results

Sociodemographic characteristics of the study population

During the study period, a total of 1,815 dermatology consultations were recorded at our study site with 41 cases of herpes zoster first and single episode during the study period, hence a prevalence of 2.3%. Three patients refused to take part in this study, giving a response rate of 92.7%.

Table 1 depicts the sociodemographic background of the study population. The sample was predominantly made of females (30/38; 78.9%), with a male/female sex ratio of 0.27/1. Ages of participants ranged from 21 to 70 years, with a mean of 39.7 ± 12.6 years. The most represented age group was 25-44 years (22/38; 57.9%). Twenty-four patients (63.2%) had attended not more than the secondary school, and 17 participants (44.7%) were singles.

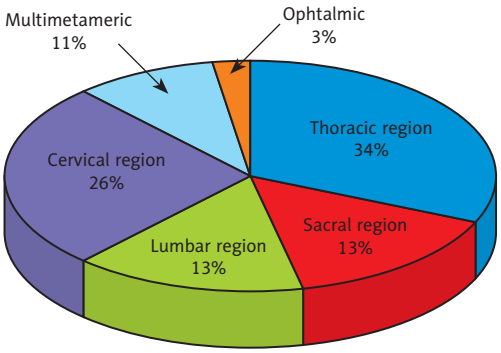

Figure 1. Localization of herpes zoster lesions

Clinical and biological profiles of patients

Herpes zoster had enabled the diagnosis of HIV infection in 23 patients (60.5%). Eight (21.1%) of the 15 patients who were HIV-infected were on continuous antiretroviral treatment. The median CD4 count was 186 (70-316) cells/mm^3, with ranges from 5 to 602 cells/mm^3. Twenty-nine patients (76%) had a CD4 count less than 350 cells/mm^3.

Twenty-six patients (68.4%) were presented with active cutaneous lesions; 11 patients (28.9%) came to consult for pain (AZN), and one patient (2.6%) for skin scars. Figure 1 is a representation of the topographic distribution of herpes zoster lesions. Lesions predominated on the chest (13/38; 34.2%); a multi metameric localization was reported in 4 cases (10.5%). The different types of lesions were: vesiculobullous (47.3%), ulcero-crusty (31.6%), and scary (21.1%). The AZN was present in all participants; its intensity was mild (1/38; 2.6%), moderate (8/38; 21.1%), or severe (29/38; 76.3%).

Treatment aspects

Twenty patients (52.6%) received acyclovir as the specific antiviral treatment, among whom 10 persons (50%) initiated the drug less than 72 hours from onset of symptoms. The drug was taken by oral route once daily for 10 days. Thirty-seven patients (97.4%) were prescribed an analgesic treatment: level 1 (5/38; 13.5%) and level 2 (32/38; 86.5%); no level 3 analgesic was prescribed. A combination of antibiotics and/or antiseptics and/or anxiolytics was initiated in 15 patients (39.5%), according to complication presented.

Twenty-two patients (57.9%) had concomitantly used traditional pharmacopeia, 5 of whom were also receiving acyclovir. Some patients had received non-pharmacological therapies, mostly consisting of psychological and spiritual support. Moreover, a patient benefited from physiotherapeutic massages.

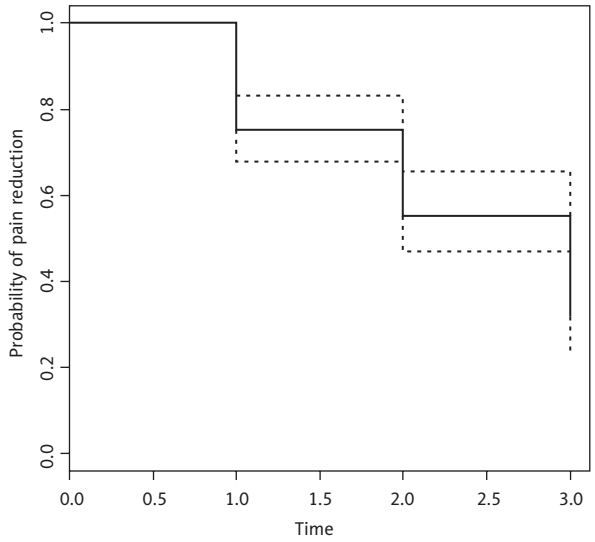

Figure 2. Evolution of pains over time (0 corresponds to the initial contact, 1 corresponds to the first visit at 15 days, 2 corresponds to the visit at one month and 3 corresponds to the visit at two months; the broken lines represent the 95% confidence interval of the curve)

Evolution and outcome

We noticed a decrease in the proportion of patients still complaining of pain after each follow-up visit, but the difference was not significant between patients on acyclovir and their acyclovir-naïve counterparts (Table 2). Table 3 shows evolution of pain intensity throughout the follow-up period. Nine patients (9/17; 52.9%) were still feeling a severe pain at the third visit, only two of whom were on acyclovir (22.2%).

Figure 2 displays evolution of PZN over time. Using the Cox regression analysis, we found that acyclovir treatment did not reduce significantly the duration of AZN (HR = 2.31; 95% CI: 0.93-5.76; $p = 0.07$). Similarly, the reduction in pain was neither related to age (HR = 0.98; 95% CI: 0.98-1.02; $p = 0.33$) nor to sex (HR = 2.54; 95% CI: 0.72-9.01; $p = 0.15$). Complications were recorded in 19 cases (50%) as pain (12/19; 63.2%) and impetiginization (7/19; 36.8%).

Discussion

This study revealed an intra-hospital herpes zoster prevalence of 2.3%. Herpes zoster diagnosis permitted to detect 23 unknown HIV-infected patients (60.5%). Twenty-six patients (68.4%) presented active dermatologic lesions; the main localization was the thoracic region (34%), and the main types were vesiculobullous (47.3%) and ulcerocrusty lesions (31.6%). All patients initially complained of moderate to severe pain. A reduction in the proportion and intensity of pain was noticed over the follow-up period, though with no difference between patients who took the specific antiviral treatment (acyclovir) and those who did not. Nevertheless, the severity of pain observed in this study calls for more attention from clinicians when managing these patients, notably the constant need to prescribe and adapt the analgesics to the intensity of pain.

Our sample was mainly made of females (78.6%), with a male/female sex ratio of 0.27/1. Concurring these results, Onumu *et al.* found a female predominance in their Nigerian study, though at lower proportions (male/female sex ratio 0.74/1) [10]. This can be explained by a feminization of the HIV pandemic. The mean age of 39.7 years approaches what was found elsewhere (35 years) [1, 10]. Similarly, the most represented age group (25-44 years) was also reported by Abdelmalek *et al.* in Tunisia [1]. Evidence has indeed shown that our young adults represent one of the most vulnerable populations with respect to HIV infection, due to elevated risky sexual behaviors [11].

Herpes zoster occurrence is the testimony of an immunodeficiency, especially among HIV-infected patients who are thereby categorized in stage B of the 1993 CDC clinical classification of HIV/AIDS [1]. In this study, the CD4 counts ranged from 5 to 602 cells/mm^3, not far from what Njamnshi *et al.* reported in Cameroon in 2006 [7], which permits to suppose that herpes zoster can occur at various stages of immunodeficiency.

Herpes zoster permitted to diagnose HIV infection among 23 patients (60.5%). Eight patients (21.1%) were already on continuous antiretroviral therapy, four of which developed herpes zoster within 3 months after initiation of their antiretroviral therapy, with CD4 counts varying from 5 to 362 cells/mm^3. Herpes zoster can indeed be the mode of revelation of HIV infection, and can also be observed during immune reconstitution after initiation of highly active antiretrovirals [12, 13].

Herpes zoster lesions can appear on any dermatome. Corroborating our results, Yamakawa *et al.* reported the chest as the main site of herpes zoster lesions (50-70%) [14]. The same authors observed that the cranial, cervical, and lumbar dermatomes were affected in 10-20% of cases [14]. We recorded 11% of multi metameric localizations; 75% of these patients had a CD4 count less than 200 cells/mm^3. These findings align to Belec *et al.'s* ones highlighting that the multi metameric nature of herpes zoster lesions is in favor of a highly depressed immune status [15].

A nucleoside analog, acyclovir, was prescribed to 20 (52.8%) of our patients for 10 days. These were patients who could afford this treatment, given their financial means. This treatment was initiated within 72 hours after onset of symptoms among 50% of these patients, reflecting the literature [16, 17]. The other 50% started their treatment after 72 hours, perhaps explained by the fact that about 58% of participants first resorted to traditional pharmacopeia before reaching the hospital. In fact, herpes zoster is still considered of mystical origin in Cameroon. Consequently, patients will primarily seek for care from traditional healers and other naturopathic doctors, and will reach the hospital generally one week after onset of eruptions, in a context of intense neuralgia and/or impetiginization.

Table 2. Proportion of patients still presenting pain at every follow-up visit

	Patients on acyclovir (*n* = 20)		Acyclovir-naïve patients (*n* = 18)		*p*-value
	Presence of pain		Presence of pain		
	Yes (%)	No (%)	Yes (%)	No (%)	
First evaluation (at two weeks)	13 (46.4)	7 (70)	15 (53.6)	3 (30)	0.18
Second evaluation (at one month)	8 (40)	12 (66.7)	12 (60)	4 (33.3)	0.09
Third evaluation (at three months)	6 (35.3)	14 (66.70)	11 (64.7)	7 (33.3)	0.05

Table 3. Intensity of pain at each follow-up visit

	Intensity of pain	Initial pain, *n* = 38		First visit, *n* = 28		Second visit, *n* = 20		Third visit, *n* = 17	
		n	%	*n*	%	*n*	%	*N*	%
Patients on acyclovir	Mild	0	0	1	50	2	100	3	60
	Moderate	3	37.5	5	55.6	2	40	1	33.3
	Severe	17	58.6	7	41.2	4	30.8	2	22.2
	Total	20	52.6	13	46.4	8	40	6	35.3
Acyclovir-naïve patients	Mild	1	100	1	50	0	0	2	40
	Moderate	5	62.5	4	44.4	3	60	2	66.7
	Severe	12	66.7	10	58.8	9	69.2	7	77.8
	Total	18	47.4	15	66.7	12	60	11	64.7

All patients complained of pain during the first consultation; the intensity was moderate in 21.1% of cases, and severe in 76.3% of cases. Patients were prescribed level 1 and/or level 2 analgesics, depending on pain intensity. Anxiolytics and/or anti-depressants were prescribed in case the analgesics were unsuccessful. Moreover, patients' financial constraints limited rigorous application of the conference consensus on anti-infectious therapeutics [16]. Our results confirm the disabling nature of herpes zoster related pain, and highlight the constant need for the physician to keep in mind the proper management of pain when treating herpes zoster-affected patients.

The acyclovir therapy did not significantly reduce the duration and intensity of herpes zoster related pain. By contrast, Wood *et al.* showed that acyclovir accelerated the disappearance of acute pain [18]. Our inconclusive results could be explained by the small sample size added to the short duration of follow-up. Furthermore, none of age and sex influenced the decline in the proportion and intensity of pains. These results do not reflect those from Rentier *et al.* who showed that herpes zoster related pain tend to be more severe and prolonged among patients aged 60 years and above [19]. Pain and impetiginization were the most frequent complications recorded. Likewise, Njamnshi *et al.* in their study found neuralgia as the most frequent complication, in 57.1% of cases [7].

Unfortunately, this study presents some limitations, these being essentially the small sample size and the short duration of follow-up. Besides, a case-control study could have been a better design to seek for factors impacting herpes zoster related pain with more reliability. Our patients were recruited from only one study site, hindering perhaps the translatability of our results to the entire Cameroonian HIV-infected population. Nonetheless, our study site is one of the biggest HIV clinics in Cameroon, with almost 40,000 patients regularly followed up and coming from Yaoundé and its surroundings.

Conclusions

The intra-hospital prevalence of herpes zoster reached 2.3% in this study. Active dermatologic lesions constituted the most frequent clinical presentation; the thoracic and cervical regions were the predominating sites of lesions. Herpes zoster enabled the diagnosis of HIV infection in most cases and seems to occur at various stages of HIV-induced immunodeficiency. The intensity of herpes zoster-related pain was mostly moderate or severe. The antiviral treatment did not impact the disappearance and severity of pain. Further studies with larger sample sizes and longer duration of follow-up are warranted to better assess all the factors impacting the decline in herpes zoster-related pain in our context.

Ethics approval and consent to participate

An ethical clearance was granted by the Ethical Review Board of the Faculty of Medicine and Biomedical Sciences, University of Yaoundé I, Cameroon. Additionally, an authorization was obtained from the Director of the Yaoundé Central Hospital. All aspects and procedures in relation with the study were fully presented to each potential participant; we included only those who voluntarily accepted to be enrolled. Every participant has signed an informed consent form.

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Conflict of interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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