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Ranulas: possible signs for HIV/AIDS? 1 year Ugandan descriptive study

ADRIANE KAMULEGEYA[1,2] & SAMUEL MOSES OKELLO[3]

[1]*Oral Maxillofacial Unit, New Mulago Hospital, Kampala, Uganda,* [2]*Department of Dentistry, College of Health Sciences, Makerere University, Kampala, Uganda, and* [3]*St Marys Hospital, Lacor Box 180, Gulu, Uganda*

Abstract

Introduction. Certain oral manifestations signal progression of HIV disease among HAART naïve patients or an increase in the plasma HIV-1 RNA levels for those on treatment. Ranulas may be one of those manifestations. Therefore, this study describes the clinical features of patients who presented with ranulas including their demographics, HIV sero-status and the CD4 CD8 cell counts for those who were HIV positive. ***Methods.*** A prospective study on ranulas was undertaken at Mulago national referral hospital and St Mary's hospital Lacor covering the period December 2008 to November 2009. ***Results.*** Fifty-seven cases participated in the study: 38.6% male and 61.4% female. Out of the study group, 73.7% were HIV positive. This was statistically significant (Chi = 12.789, df = 1, $p = 0.001$). In relation, to CD4 cell count, 23.8% had <200 cells/mm^3, 35.7% between 200–500 cells/mm^3 and 40.5% more than 500 cells/mm^3. The CD4-to-CD8 ratio ranged from 0.02–0.98 with an average of 0.31 ± 0.23, median and mode of 0.27 and 0.32, respectively. ***Conclusions.*** It is felt that ranulas may be one of the oral manifestations of worsening immunity in HIV/AIDS disease. Therefore, more research is needed to establish if it should be included among known oral manifestations of the disease.

Key Words: *ranulas, HIV, AIDS, Mucocele, salivary gland disease*

Introduction

It is estimated that up to 90% of persons with human immunodeficiency virus (HIV) infection, at some stage present with at least one oral manifestation of the disease [1,2]. Additionally studies have shown that oral manifestations of HIV increase with worsening immunologic impairment either with or without a fall in CD4 lymphocyte count. Likewise they signal an increase in the plasma HIV-1 RNA levels among patients on HAART. Therefore, identification of such lesions could be of prognostic and management significance [3–6]. Although regional differences in oral manifestations seen in HIV/AIDS patients have been reported, globally oral candidaisis is the most universal and commonest opportunistic infection. Kaposi's sarcoma has been reported mainly from Africa and Latin America, while histoplasmosis and penicilliosis are reported in patients with advanced disease in Thailand [7,8]. Additionally major advances in human immunodeficiency virus (HIV) care have resulted in improved survival and a decrease in incidence of opportunistic infections (OIs) for individuals receiving highly active anti-retroviral therapy (HAART) [9,10].

Salivary gland diseases are one of the manifestations associated with HIV/AIDS. The diseases include a vast range such as lymphomas, lymphadenopathy with in parotid gland, parotid cysts, parotitis, Syjogren's like syndrome, Sicca complex and HIV associated salivary gland disease. The etiology and pathogenesis of these salivary gland conditions are still unknown [11–13]. More recently studies from Zimbabwe, South Africa and Kenya reported ranulas as a potential oral lesion in HIV/AIDS [14–16]. A potential explanation for ranulas among HIV/AIDS cases was attempted [17].

Uganda, just like Zimbabwe, South Africa and Kenya, has a high burden of HIV/AIDS prevalence, estimated at ~ 6.4% with over 80% of those infected being unaware of their status [18]. Therefore, alertness to rare conditions that occur among HIV/AIDS patients may be a key step in initiating counseling and testing. We decided to conduct a 1-year prospective

Correspondence: Dr Adriane Kamulegeya, DDS M Clin Stomat OMFS, College of Health Sciences, Makerere University, Dentistry, box 7072, Clin res Bldg, Kampala, Uganda. Tel: +256712072432. E-mail: adrianek55@gmail.com

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study to determine the prevalence of HIV among ranula patients who came to Mulago Hospital, Kampala, and St Mary's hospital Lacor, Gulu, Uganda during the period November 2008–October 2009. We also wanted to establish the CD4 CD8 cell counts of those who were found to be positive so as to establish a relationship if any. Furthermore, we wanted to determine if ranuli should be included among possible oral manifestations of HIV/AIDS in Uganda.

Methods

This was a cross-sectional descriptive study which included 57 ranula patients that were seen at Mulago Hospital, the national referral medical facility of Uganda, which also serves as a primary hospital for greater Kampala and St Mary's hospital, Lacor, a well facilitated missionary hospital that serves the catchment area of Gulu and surrounding northern Uganda districts (22 patients). All patients who presented with Ranuli in these two centers during the study period were counseled and informed of the study objectives. It was made clear to them that they could opt out. They were assured that either choice would not affect their treatment. Seventeen patients opted out. Fifty-seven consented by either revealing their HIV status or agreeing to voluntary counseling and testing. For those who were not aware of the HIV status, tests were done using the rapid test Determine HIV-1/2/O (Abbott Laboratories, Abbott Park, IL). Negative and positive tests were handled as described by Gray et al. [19]. Confirmation of weak positives was done using enzyme immunoassay or western blot. The HIV/AIDS status of infants 18 months and below was confirmed by virology assays using reverse transcription Polymerase chain reaction (PCR).

Those who were found to be HIV positive were requested to have CD4 and CD8 (cells/mm^3) counts done. Patients who reported their status as positive were asked to provide documentary evidence and the last CD4 CD8 counts. Most of these patients were referrals from HIV/AIDS treatment centers so access to the CD4 and CD8 was got from their care centers. The CD4 CD8 count was taken if it had been done within the last 3 months, while anyone whose results were older than that was asked to have a CD4 CD8 count done before treatment of the ranula. As per the information from the different centers, CD4 counts were assessed by flow cytometry. Clinical diagnosis of ranulas was done by doctors who had been in Mulago handling these cases for at least a year.

The study was approved by the respective institutional review boards and all patients whether in or out of the study were treated free of charge. The main stay of treatment was marsupialization through an intra-oral sublingual approach. The cavity was packed with sterile gauze impregnated with petroleum jelly, zinc oxide powder (Scitem International, London, UK) and iodofoam paste (Produits Dentaires SA, Vevey, Switzerland). The gauze was reduced after day 3 and removed within a week. The recurrences were treated by sublingual gland extipation.

The results were processed with SPSS Win 15 and associations between variables were analyzed using non-parametric chi-square; p-values less than 0.05 were considered significant.

Results

A total of 57 cases participated in the study during the study period: 38.6% ($n = 22$) male and 61.4% ($n = 35$) female, with a male-to-female ratio of 1:1.6. There was no gender preponderance (Chi = 2.96 df = 1, $p = 0.85$). The age range was from 1–50 years, with an average of 18.6 ± 12.2. Figure 1 shows the gender and age distribution. We saw five (8.7%) plunging ranulas, i.e. with an oral and submandibular extension, the rest were intra-oral, restricted to the sublingual region Figure 2 shows pictures of a plunging and bilateral intra-oral ranula from some of our patients. The left sublingual gland was the most commonly affected, accounting for 63.2% ($n = 36$), with one case seen that involved both sides (Chi = 32.32, d = 2, $p = 0.001$). The self-reported duration of the swellings ranged from 1–104 weeks with a mean time of 10.3 ± 16.5 weeks, mode and median of 4 and 5 weeks, respectively. Following treatment until the time of writing this report we had two cases of recurrence.

Out of the study group of 57 patients, 73.7% ($n = 42$) were HIV positive. This was statistically significant (Chi = 12.78, df = 1, $p = 0.001$). All those who were HIV positive provided us with CD4 and CD8

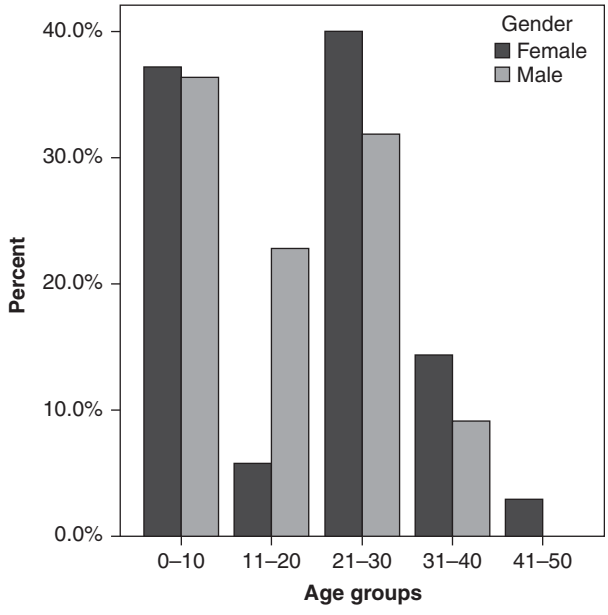

Figure 1. The gender and age distribution.

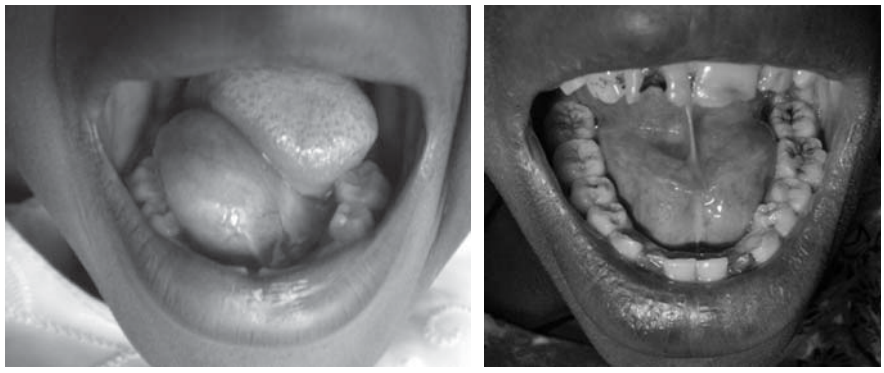

Figure 2. A typical intra-oral ranula and a plunging one.

cell count before treatment. The age groups 1–10 and 21–30 years with equal distribution accounted for the highest number, 35.7% (n = 15 each), as shown in Table I (chi = 29.05, df = 4, p = 0.001). Of those who were HIV positive, 35.7% (n = 15) were on highly active anti-retroviral therapy (HAART), with three of them being on second line HAART, while only 4.8% (n = 2) were taking Co-trimoxazole (Septrin) Prophylaxis. The rest reported not having had prior knowledge of theirs HIV sero status.

In relation to CD4 cell count, 10/42 (23.8%) had <200 cells/mm^3, 15/42 (35.7%) between 200–500 cells/mm^3 and 17/42 (40.5%) more than 500 cells/mm^3. The HIV positive ranula patients' CD4 values on and off treatment are shown in Table II. The mean CD8 cell count was 1552.5 ± 786 cells/ml with a range of 514–5184 cells/ml. Of the 10 patients with CD4 cell count 200 and below, eight didn't know their status.

The CD4-to-CD8 ratio ranged from 0.02–0.98, with an average of 0.31 ± 0.23, median and mode of 0.27 and 0.32, respectively.

Discussion

Prevalence studies of HIV-associated oral lesions have been conducted at sites to which patients have either been referred for evaluation of existing lesions or among individuals belonging to specific transmission categories and HIV/AIDS support groups and treatment centers [5,8,10,20,21]. However, ranulas as a HIV associated lesion have not been extensively reported except for case reports and studies from Zimbabwe. However, recently more publications from South Africa and Kenya have added impetus [14–16]. Those studies, just like this one, were all done in referral centers and thus may not reflect the prevalence of lesions found in the general HIV infected population; however, they provide anecdotal information of what could be happening and as such provide useful research information. A study by Tiromwe et al. [20], at TASO clinics in Uganda, didn't report ranulas as a manifestation of the disease. However, they were using the WHO form for oral manifestations of HIV/AIDS [22] which doesn't have ranulas as one of the manifestations to look out for and hence they could easily have missed it. Since this entity has been reported by studies from Zimbabwe, South Africa and Kenya, which are reports indicating geographic area-specific oral manifestations of HIV/AIDS [7,8,14–16], further studies in oral health care centers within Africa and other less developed countries are needed to establish whether this is just peculiar to East and Southern Africa.

The male-to-female ratio in this study was 1:1.6, which is close to the 1:1.3 reported from Zimbabwe [14], p = 0.41. This also corresponds with the HIV incidence male-to-female ratio of the country as reported by Hladik et al. [18]. However, when the male-to-female ratio of patients who presented with ranulas and were HIV positive was considered, it was 1:1.8. This finding is similar to what was reported from Kenya [16]. Whether HIV females are more

Table I. Age group distribution and sero-status of the study subjects.

	HIV sero status		
Age group	Positive	Negative	Total
0–10	15	6	21
11–20	5	2	7
21–30	15	6	21
31–40	6	1	7
41–50	1	0	1

Table II. The CD4 cell counts of the 42 patients who were HIV positive.

	Treatment being given			
CD 4 cell count category	Non	Co-trimoxazole	HAART	Total
<200	2	0	8	10
200–500	13	2	2	17
>500	10	0	5	15
Total	25	2	15	42

likely to get ranulas needs more research involving bigger numbers of patients.

In the present study the 1–10 and 21–30 year age groups in both males and females were the most commonly affected, which was different from the Zimbabwean experience of ranulas that reported over 70% as being in the 0–10 year age group [14]. Additionally in both groups 71.4% were HIV positive, as can be seen in Table I. In Zimbabwe [14] the high prevalence of ranulas and HIV among the 0–10 years group was attributed to mother-to-child transmission. This may be the same reason in our study when it comes to the 1–10 years age group.

Although HIV/AIDS has been reported not to play a direct role in causation of salivary gland disease [23], it seems to have some role in increased incidence of diseases such as Sjogren's syndrome, bilateral parotid swellings among infected patients [11,24]. More recently some retroviral drugs have been reported to have the same effect as certain salivary gland diseases [2,15]. Different explanations for high prevalence of ranula among HIV/AIDS patients have been given, ranging from infiltration of CD8, falling CD4 cell count and protease inhibitor retroviral drugs [17,24,25]. In this study due to lack of funds we didn't have the CD4 and CD8 count for negative patients nor did we test for CD8 infiltration into the glands of both HIV positive and negative patients which would have been very helpful in establishing the role of CD8.

Table II shows the CD4 cell count distribution of our HIV positive patients. As seen in the table we had a group of less than 200 cells/μl count because it's the threshold of starting treatment in most Ugandan centers [26] and there was no statistically significant difference ($\chi^2 = 1.85$, df = 2, $p = 0.39$). As improvements and increasing options available in HIV care take root, the threshold for CD4 levels before starting treatment has been revised up to below 350 cells/μl [27], therefore we did further analysis which showed that 18 (42.9%) had CD4 cell ≤350 and still there was no statistically significant difference between occurrence of ranuli and CD4 cell count ≤350 ($\chi = 0.85$, df = 1, $p = 0.35$). However, it's important to note that of the 18 patients who had CD4 cell count below 350, 15 were naïve about their status. Decline in CD4 cell count is reported to have a relationship with HIV/AIDS oral manifestations and a combination of low CD4 cell count and certain oral manifestation are good indicators of disease progression [1,28,29]. However, it should be noted that some manifestation of AIDS are independent of CD4 cell count but rather reflect an increase in Viral RNA [3–6], unfortunately we didn't have viral load results. Therefore, although there was no statistically significant relationship between falling CD4 cell count and presence of ranulas, we feel the presence of a ranula should warrant HIV sero-status testing and, if found positive, CD4 cell count should be requested. This is because some of our patients had low CD4 cell counts without any other symptoms, hence ranulas may be a starting point for HIV/AIDs treatment initiation. Hopefully better planned, financed and multi-centered research will be carried out to establish the relationship if any between HIV/AIDS, CD4 cell count, viral load and ranulas, so as to either add or rule them out as AIDS-defining symptoms in HIV positive patients.

The average CD4/CD8 ratio in our study was below the expected national medians of a HIV negative population [30]. In fact for all patients the ratio was below one (mean = 0.31 ± 0.23, range = 0.02–0.98, median = 0.26, mode = 0.32). The low ratio is indicative of either a decrease in CD4 cell count, increase in CD8 or both. The median CD4 and CD8 cell count of the HIV positive patients in our study were 490 and 1365, respectively. Both values were below the medians of the different normal age group categories reported by Lugada et al. [30]. Due to small numbers we didn't analyze the medians of our patients using groupings as in Lugada et al. [30]. However, the overall median shows that our ranuli patients who were HIV positive had changes in both their CD4 and CD 8 values. Low CD4/CD8 ratio has been associated with some diseases such as myocardial infarction [31]. Whether the low CD4/CD8 ratio is the explanation for ranulas in HIV patients needs some more investigation, with tests run for those who have ranulas yet are HIV negative, so as to enable comparison.

Conclusions

Just like reports from Zimbabwe, South Africa and Kenya, we feel ranulas may be one of the oral manifestations of worsening immunity in HIV/AIDS disease and warrant more research to establish if it should be included among known oral manifestations of the disease. A multi-center study is needed, especially in sub-saharan Africa where the bulk of the disease is.

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