

The potential impact of highly active antiretroviral therapy on the treatment and epidemiology of ranula in HIV-positive patients.

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Abstract

Objective. The study's aim was to assess the potential therapeutic effect of highly active antiretroviral therapy (HAART) on ranulas in HIV-positive patients.

Study design. The study includes a retrospective observation of three patients who were initially part of a prospective study on the comparative effect of HAART on ranulas in 14 HIV-positive patients. These patients were clinically monitored while pursuing the medical treatment with HAART. Neither a fine needle aspiration (FNA) nor a surgical operation was performed. Clinical photographs were used for monitoring of any reduction in the ranula size. The effect of HAART on ranula was assessed at 3, 6 and 12 month.

Results. A complete resolution of the ranula lesion was noticed in the three HIV-positive selected patients. These results were observed between 6 and 12 months period.

Conclusion. This study suggests that HAART might present a potential therapeutic effect on ranula in HIV-positive patients.

Key words: HAART - Ranula – HIV

INTRODUCTION

Oral mucoceles in HIV-negative patients, including the ranula type, have been reported in numerous publications.^{1,2} The surgical approach has also been generally recognized as the main stream of treatment modality for ranula.^{1,3-7}

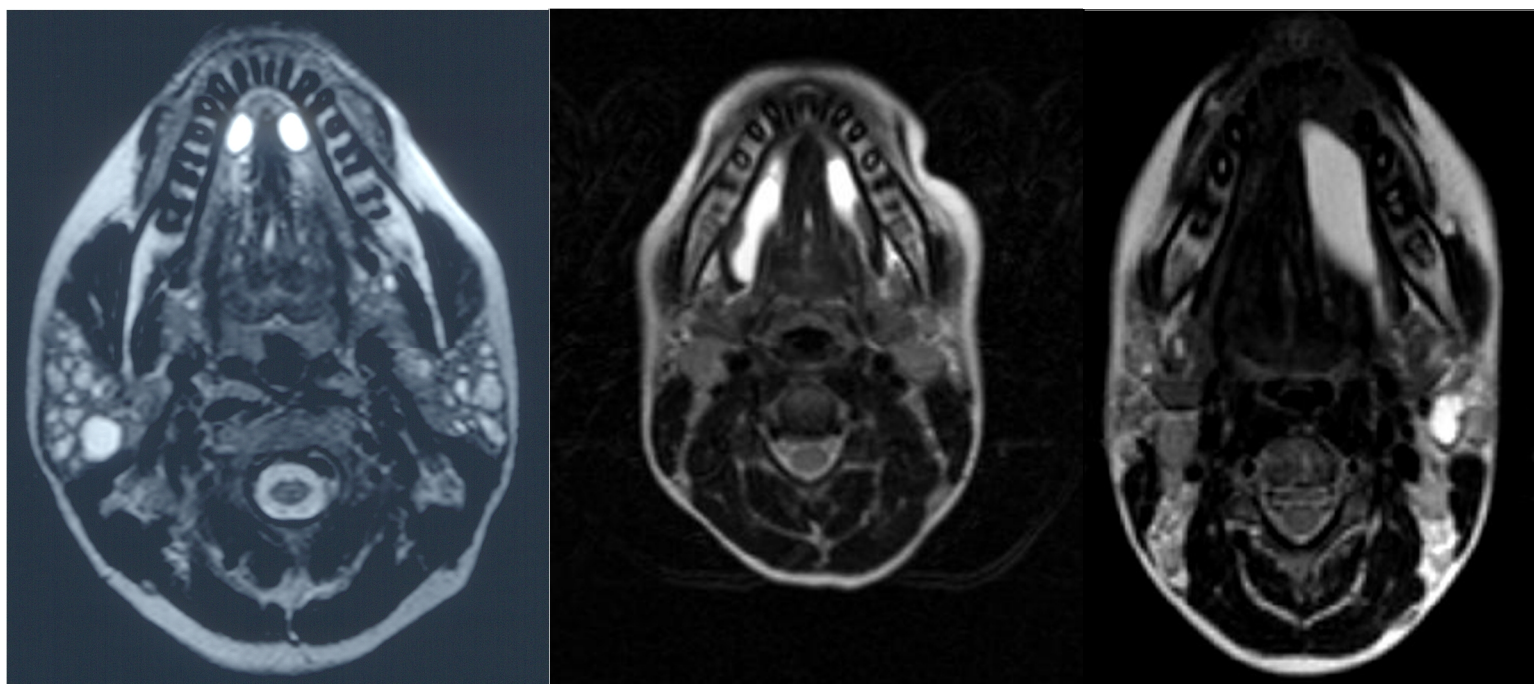
It has emerged from the literature that there is an increase in observations of the clinical association of ranula and HIV infection.⁸⁻¹⁸ The causative relationship, as well as the exact

prevalence of ranula in HIV-positive patients is still to be established. However, some specific aspects in the clinical presentation of ranula in HIV-positive patients have been identified and documented. Syebele and Bütow^{8,12} have reported the coexistence of ranula with benign lymphoepithelial cyst (BLEC) of the parotid gland in the same HIV-positive patient. These authors have also noted a substantial number of plunging and bilateral ranula amongst HIV-positive patients (Fig. 1A, B and C). These latter clinical characteristics of ranula have highlighted the limitation of the surgical approach and created the need to explore other non-radical modalities of treatment for ranula in HIV-infected patients. Indeed, there would be limited rationale for the surgical removal of several affected salivary glands, as they appear in some HIV-positive patients. The preservation of salivary flow in HIV-infected patients is of paramount importance in this specific group of patients in whom xerostomia has been documented and reported.¹⁹

There is, to the best of our knowledge, no evidence based literature describing the effect and long-term result of HAART on ranula. The present article aims to consolidate the previous observation suggesting that ranula in HIV-positive patients, similar to lymphoepithelial cyst of the parotid gland, could also benefit from the indirect therapeutic effect of highly active antiretroviral therapy (HAART) in the context of HIV-related salivary gland diseases (HIV-SGD).¹²

PATIENTS AND METHODS

This study is based on the clinical observation, of three patients diagnosed HIV positive and presenting with ranula. These patients were initially part of a prospective study involving 14 HIV-positive patients.¹² Based on the preliminary results of “positive change” observed in



1A

1B

1C

Fig.1. MRI imaging (axial views) at the level of the floor of the mouth. **(1A)** shows bilateral ranulas in both sublingual areas, and bilateral parotid glands with multiple lymphoid infiltrations. A HIV-related cystic image can also be seen in the right parotid.**(1B)** presents a case of bilateral plunging ranula. **(1C)** presents another case of combination of ranula with parotid gland lymphoid infiltration with a starting cystic lesion.

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patients No 7, 13 and 14 during the assessment term of between three and six months (Table 1), it was decided to continue with the clinical observation of these subjects. The final evaluation of the three patients was done at 12 months term from the start of HAART.

Patient's consent for continuous clinical observation, and sustained compliance with HAART medication beyond the initial timeframe of 6 months were a prerequisite. The three subjects were requested to remain under HAART without any invasive procedure (fine needle aspiration (FNA), open biopsy or surgical operation) being performed on them. The diagnosis of ranula was based on clinical examination.

Owing to the unstable and cystic nature of ranula, it was not practical to express measurements in centimeters. The effect of HAART on ranula was assessed clinically by monitoring any reduction in the size of the ranula. A complete or partial size reduction of the ranula was considered to be a positive result. Comparative clinical photographs were used for monitoring purpose, from the start of HAART up to the final results.

Ethics and informed consent

The initial prospective study (Oral Surg Oral Med Oral pathol Oral Radiol Endod 2011;111:205-210) was conducted with strict adherence to all regulations and guidelines governing the research and the management of HIV-positive patients in South Africa. The protocol and informed consent documents were reviewed and approved by the Faculty of Health Sciences Research Ethics Committee, University of Pretoria.

Table 1. Socioepidemiological data and clinical results for 14 patients with ranulas

	SEX	AGE	INITIAL CD4 <i>x10⁶/l</i>	INITIAL VIRAL LOAD <i>RNA copies/l</i>	RANULA TYPE	HAART REGIMEN	RESULTS AFTER 3 MONTHS	RESULTS AT SIX MONTHS	RESULTS AT TWELVE MONTHS
1	M	13	31		PLUNGING	D4T+3TC+EFV	No change	NO change	
2	F	39	54	17000	SIMPLE	D4T+3TC+EFV	No change		
3	F	31	92	24000	PLUNGING	D4T+3TC+EFV	No change		
4	M	39	121	46000	PLUNGING	D4T+3TC+EFV	No change		
5	F	29	207	20000	PLUNGING	D4T+3TC+EFV	No change		
6	F	50	251	93000	SIMPLE	D4T+3TC+EFV	No change		
7	F	32	287	74	PLUNGING	D4T+3TC+EFV	No change	Partial positive change	Complete resolution
8	F	27	302	5500	PLUNGING	D4T+3TC+EFV	No change		
9	F	23	324	130000	SIMPLE	D4T+3TC+EFV	No change	NO change	
10	F	42	339	8300	PLUNGING	D4T+3TC+EFV	No change	NO change	
11	F	32	357		PLUNGING	D4T+3TC+EFV	No change		
12	M	6	400	290	SIMPLE	D4T+3TC+EFV	No change		
13	F	6	521	<25	SIMPLE	D4T+3TC+EFV	No change	Partial positive change	Complete resolution
14	F	2	972	150000	SIMPLE	D4T+3TC+EFV	No change	Partial positive change	Complete resolution

D4T=Stavudine, 3TC=Lamivudine, EFV=Efavirenz.

RESULTS

The socioepidemiologic data and clinical results from the prospective 14 patients presenting with ranulas are summarized in Table 1. Patients No 7, 13 and 14 displayed a partial positive result at 6 months' assessment. A complete resolution of ranula on these three patients was observed at 12 months assessment. The clinical reduction in the size of the ranula (Fig. 2A, 2B, 2C, 2D and Fig. 3A, 3B) was slow and gradual. The final results of patients 7 and 13 are represented in Fig. 2D and 3B.

DISCUSSION

The association of HIV infection with oral mucoceles, especially the ranula type, has been reported by various authors. The majority of these cases, for reasons not yet explained, have been observed in sub-Saharan Africa.⁸⁻¹⁸ The causative link between HIV infection and ranula remains to be elucidated. The ranula is currently considered in some quarters as a lesion frequently associated with HIV infection, and it may also be the initial manifestation of an underlying HIV infection.^{8,9,15,16}

The surgical removal of the ipsilateral sublingual salivary gland, with or without the dissection of the pseudo cystic wall remains the most accepted form of treatment for ranula.^{1,3-7} . Nevertheless, some complications associated with the surgical management of ranula have been reported in the literature.²⁰ The clinical presentation of ranula in some HIV-infected patients, specifically the involvement of more than one salivary gland and the observation of a ranula coexisting with a BLEC of the parotid gland in the same patient (Fig. 1A, B and C) highlight the limitation in the feasibility of the surgical approach.¹² The young age of some patients who are also affected by the HIV-SGD should be considered.^{8,14} The need to explore other non-surgical



Fig.2. Case No 7 - A simple ranula in the floor of the mouth: (2A) before HAART. (2B and 2C) after treatment with HAART for up to six months, without any FNA performed. (2D) clinical complete resolution of the ranula in the same patient as in Fig. 2A at 12 months assessment period.

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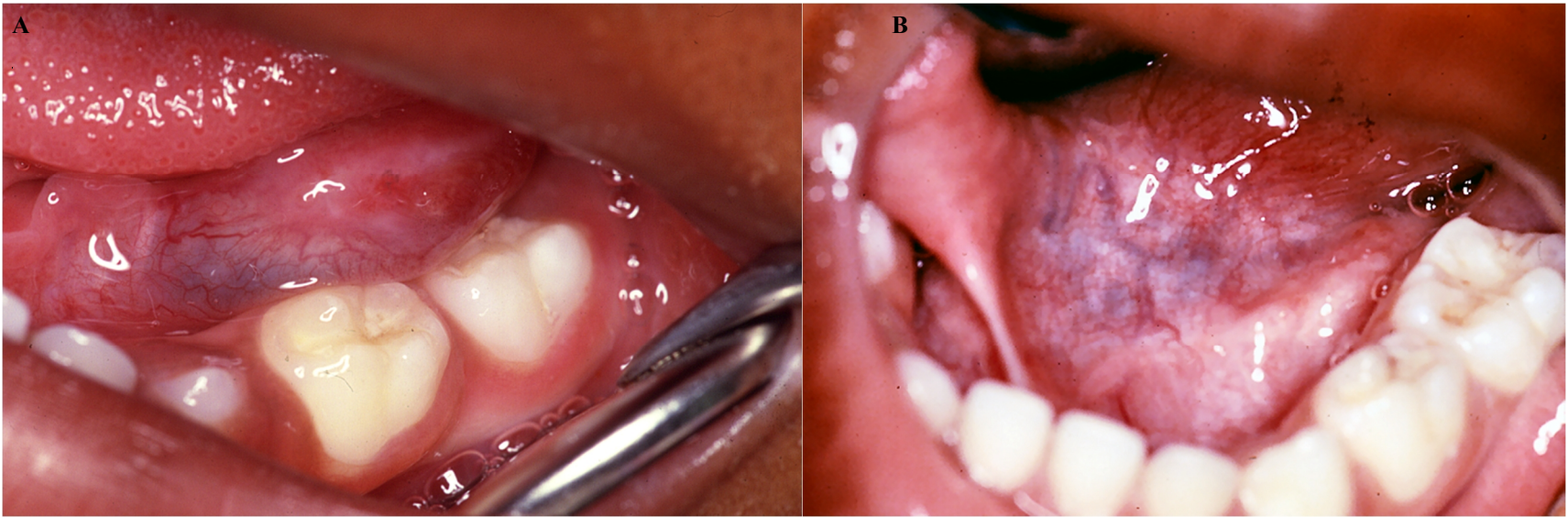


Fig.3. Case No 14 - (3A) ranula before HAART and (3B) final result at one year assessment.

modalities of treatment for ranula in the particular context of HIV-positive patients is therefore justified.

Several non-surgical approaches for the management of ranula in HIV-negative patients have been described in the literature, with variable results.^{21,22} Unfortunately, both the surgical removal of the sublingual salivary gland, and the use of any other intra lesional treatment of ranula in HIV-positive patients will remain a limited approach, that does not interfere with the systemic context of HIV. Therefore, the provision of a non-surgical treatment should, preferably be an integral part of the overall therapy of the HIV-infected person. The treatment should not only solve the ranula problem, but it should also improve the overall health and the quality of life of the patient.

In the present study we observed and documented a small number of patients whose ranula has effectively been influenced by HAART. The speed at which the results have been obtained was slower (6 to 12 months) compared with that observed in cases of BLEC of parotid salivary gland (3 months).¹² Nevertheless, the results described suggest that, in some cases, ranula may completely resolve under the influence of HAART.

The present authors suggest the following explanation: a reversible obstructive mechanism may be the cause of the formation of the ranula in HIV-positive patients. An obstruction created by the lymphoid infiltration as described in the diffuse infiltrative lymphocytosis syndrome (DILS), may be reversed by the implementation of HAART.²³ The demonstration of lymphoid infiltration in the biopsy of the sublingual salivary gland (CD8 cells) might have been of great support to this theory on the etiopathogenesis of ranula in HIV-positive patients. However, it remains unclear at this stage, why are not all cases of ranula responding positively to the administration of HAART. More studies are probably needed.

This result might, on the one hand, impact on the need for a surgical modality in the treatment of ranulas and more importantly may provide a solution to cases of bilateral ranulas and multi-glandular lesions (parotid, submandibular and sublingual salivary glands) in the same patient (Fig. 1A, B and C). These observations might, on the other hand, have an influence on the epidemiology of ranula in HIV-positive patients. Indeed, it is conceivable that HAART may influence the prevalence of ranula in HIV-positive patients. It is also conceivable that HAART may influence the outcome of the surgical treatment of ranula by conservative treatment such as marsupialization for example. The number of recurrences post ranula marsupialization might be reduced.

The small number of subjects remains the major weakness of this present study, and these results need to be considered with caution. However, the results highlight the potential therapeutic effect of HAART on ranula in HIV-positive patients. Furthermore, the following hypothetical question might be asked: may the potential therapeutic effect of HAART have an impact on the epidemiology of oral mucoceles in general and ranulas in particular.

CONCLUSION

The number of cases described in the article is certainly small and does not allow for a definitive wide conclusion. Therefore, caution is required when considering the final results as shown in Fig. 2D and 3B. These results suggest that HAART seem to have acted on ranula, although at a slower pace than that reported for BLEC of parotid gland. The current authors recommend that HAART should be tried before any aggressive modality of treatment is implemented, especially on those patients who qualify, or are already under the therapy.

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