Oral Mucosal Lesions in a UK HIV/AIDS Oral Medicine Clinic. A Nine Year, Cross-Sectional, Prospective Study

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Purpose: To investigate changes in presentation of oral mucosal lesions in patients with HIV/AIDS attending a dedicated oral medicine clinic over a nine year period.

Materials and Methods: 358 Patients with HIV/AIDS attending a dedicated oral medicine clinic, contained within a genitourinary medicine clinic. Data was collected prospectively for all patients attending the oral medicine clinic, and entered into a database. Lesions were recorded according to the EEC-WHO diagnostic criteria 1991/1993.

Results: In 358 patients with 542 lesions, over 54% of the lesions belong within one of the five categories of ulcers, warts, candidiasis, OHL and Kaposi's sarcoma. The major differences in the presentation of the lesions over time were between the ulcers and the warts, but in this series the introduction of HAART did not make a statistical difference.

Conclusions: There has been a large reduction in the presentation of oral ulcers, and there appears to be a relative increase in viral papillomata, and a decrease of other mucosal diseases over the period of study. Many of the warts biopsied showed dysplastic changes, and continued follow-up of these patients will be important to determine whether these patients are at increased risk for developing oral squamous carcinoma. Also, proposals are put forward suggesting a need for alteration of the three groups of HIV/AIDS lesions classification suggested by the EEC-WHO consensus.

Key words: HIV, cross sectional study, oral medicine, oral lesions, HPV, oral ulcers

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The appearance of oral lesions is often a significant milestone in the progression of disease for a patient infected with the HIV virus moving towards AIDS (Greenspan, 1997). Some oral presentations are important as AIDS-defining conditions. In 1991 a consensus on the classification of, and diagnostic criteria for oral lesions in HIV infection was reached and published (Anon. 1991). This was as a result of a meeting between European and US workers and formed the basis for the diagnostic criteria of the conditions described in this study. The diagnostic criteria were again reviewed and an updated classification was later published (Anon. 1993).

Early therapy for HIV/AIDS relied on the use of single agents, for example nucleoside reverse transcriptase inhibitors such as zidovudine (AZT or ZDV). Later development in anti-retroviral agents has produced protease inhibitors and non-nucleoside reverse transcriptase inhibitors. Initially single agents were used for anti-retroviral therapy (ART), and in later years combinations of agents have been used. A permutation of a protease inhibitor or non-nucleoside reverse transcriptase with two or more nucleoside reverse transcriptase inhibitors is

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a therapeutic approach known as highly active anti-retroviral therapy, or HAART.

From the beginning of the HIV pandemic it was recognised that patients with HIV would present with oral lesions such as oral hairy leukoplakia (OHL), Kaposi's sarcoma (KS) and candidosis. The pattern of presentation of general and systemic AIDS-defining conditions has altered over the years with the increasing use of HAART, (Brodt et al, 1997) and this has been reflected also in changes in the presentation of oral lesions. (Eyeson et al, 2000; Patton et al, 2000; Schmidt-Westhausen et al, 2000). Although the presentation of many oral conditions has decreased the incidence of some lesions has been seen to rise. Interestingly, an increase in the prevalence of oral lesions has also been noted in other, non-HIV positive, immunocompromised patients (King et al, 1995). The importance and prognostic significance of HIV associated lesions has been discussed in the paper by Birnbaum et al (2002).

A recent paper by Greenspan et al (2001), demonstrated the changing pattern of prevalence of oral lesions following the introduction of HAART over a nine year period, a period comparable to this study. In general there was a decrease in the prevalence of many conditions, but for salivary gland disease and oral papillomata the prevalence was increased. The patient pool for the Greenspan paper comprises patients referred to a specialist oral medicine clinic based in California, USA. The aim of this study is to describe the oral mucosal lesions of patients with HIV/AIDS referred to a dedicated UK oral medicine clinic over a nine year period, during which time a number of new antiretroviral medications were introduced.

MATERIALS AND METHODS

The data for this study were collected prospectively from all patients attending an oral medicine clinic dedicated to the treatment of patients with HIV based in London, England. This clinic was part of a multidisciplinary genitourinary department which also included a dental clinic which had a throughput of 2050 new patients over the nine year period. Patients who perceived they had an oral problem or who were deemed to have one by their healthcare workers were referred to this specialist oral medicine clinic. Patients with periodontal problems were referred separately to a periodontal specialist, and therefore not seen in the oral medicine clinic, and so do not feature in the data collected. This data has been previously reported (Robinson et al, 1996). The majority of patients (88.6%) was referred from within the genitourinary clinic. The remainder were referred from other clinics in London. At each visit patients had a full medical and dental history taken and an examination of the oral cavity was performed. Each patient was examined by a specialist in oral medicine, and the same specialist was responsible for examining all the patients throughout the period of the study. The clinical diagnostic criteria as set out in the EEC-WHO studies (Anon. 1991; Anon. 1993) were used throughout. Patients were discharged after their lesion was treated. Patients who returned for a further consultation after the initial lesion had healed were classified as new patients. Eight per cent of patients belonged to this category with 21 patients attending twice, 5 patients three times and 1 patient four times. Biopsies were taken where necessary and all the histology was reported by the same oral pathologist throughout the study period.

In this study patients would present with 'virgin' lesions. The patients were referred for diagnosis and/or management to the specialist oral physician by genitourinary physicians. No therapy, for example thalidomide or antifungal medications, would be introduced for treatment of oral lesions prior to consultation with the oral physician. An exception to this, however, may be those patients who were already taking mediation for the treatment of candidal infections only. The same would be true for antiviral medications which patients were taking as part of their anti-HIV therapy, or, for example for genital viral lesions.

The data collected was examined by an experienced statistician using a series of repeated chi-square tests comparing the patient groups with ulcers, viral lesions, etc. The statistical package used was SPSS (Version 10.0 for Windows, SPSS Inc. Headquarters 233 S. Wacker Drive, 11th Floor, Chicago, Illinois USA).

RESULTS

The majority of patients were homosexual men. The study group comprised 358 individuals (336 males, 22 females). The mean age was 38 years (SD ±8.25 years), with a range from 22 to 68 years and patients had had HIV/AIDS for a mean of 5.07

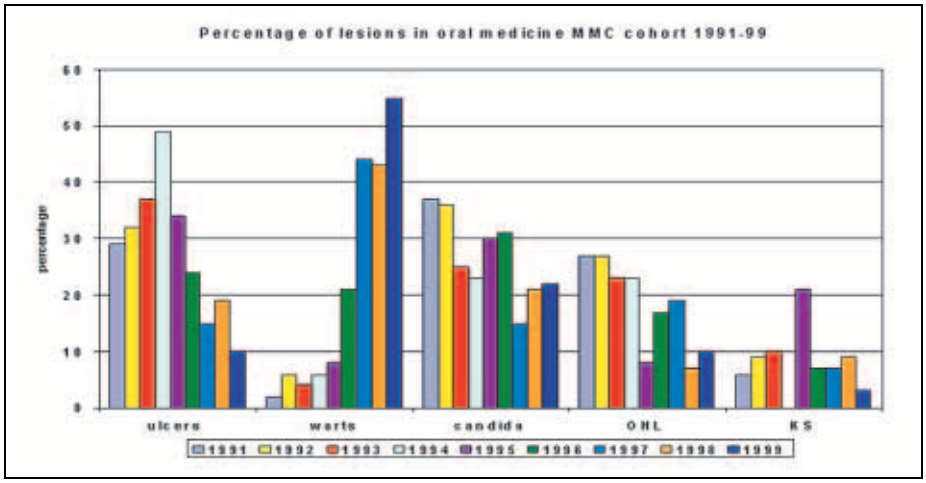

Fig 1 Percentages of lesions seen in oral medicine clinic 1991-1999. The total number of lesions was: all types of ulcers = 118, warts on clinical appearance = 80, candidal infections all forms = 105, oral hairy leukoplakia (OHL) = 77 and Kaposi sarcoma (KS) = 34.

years (SD ±3.72 years) from the time of testing. Initially many patients were only on drug therapy if their CD4 counts fell below 200 cells mm^{-3} but after 1996, with the introduction of new antiretroviral agents, patients were usually started on triple therapy. Thirty-nine patients were on triple therapy, two patients on quadruple therapy, and ninety-two on no antiretroviral therapy. Approximately 44% of patients in our cohort had CD4 counts of 200 mm^{-3} or greater. Over 54% of patients had diagnoses in the five major categories of ulcers, warts, candida, OHL, KS. On average each patient had 1.6 lesions, with a total of 542 lesions. The overall distribution of the major lesions presenting over nine years is seen in Fig 1. The ulcers described in Table 1, have previously been reported by Zakrzewska et al, 1997.

The candida lesions were divided into 4 different categories and showed a relatively even distribution throughout the reported period. There were 35 (33.3%) pseudomembranous candidosis, 32 (30.5%) erythematosus candidosis, 20 (19%) histologically confirmed hyperplastic candidosis and 18 (17.2%) angular and mixed candidosis. Amongst these patients candida was more likely to be seen in patients with low CD4 counts.

The incidence of oral ulcers varied over time and the reduction in their incidence related to the introduction of HAART. A case series of severe oral ulceration in this cohort has also been reported previously (Zakrzewska et al, 1997). Of the 118 ulcers seen, the diagnosis included: 52 (44.1%) non-specific ulceration, 38 (32.2%) recurrent aphthous stomatitis (RAS), 13 (11%) herpes simplex, 7 (5.9%) cytomegalovirus (CMV), and the remainder including 3 (2.5%) neutropenic (neutrophil count < 0.8 x 10^9 l^{-1}), 4 (3.4%) traumatic ulcers and 1 (0.8%) related to chemotherapy. The RAS type ulceration was found more frequently in the earlier stages of disease. Fig 2 shows an example of a serpiginous ulcer of CMV affecting the lateral border of the tongue. Patients may present with more than one CMV ulcer at a time, and would often present with other systemic manifestations of CMV infection e.g. retinitis and colitis. Of the patients with ulcers 7 (6%) were on triple therapy at the time of the ulceration.

Although it seems plausible to suggest that the introduction of HAART led to an increase in oral warts from 1996 onwards a chi-square test showed no correlation. The years compared were: 1991–1995 to 1991–1995 (using only patients who were on HAART in the latter period). The incidence of warts did not rise with the lowering of CD4 count or the length of duration of disease. Of the 80 warts seen, 43 (53.8%) were biopsied and of these 19 (44.2%) showed signs of dysplasia. A typical pathology report for a dysplastic wart reads as follows: 'A strip of oral mucosa covered by hyperparakeratinised stratified squamous epithelium showing raised areas composed of grossly thickened and elongated rete ridges, sometimes with bulbous morphology. There is prominent basal cell hyperplasia with pleomorphism and occasional vacuolated, koilocyte-like cells are noted in the prickle cell layer. The lamina propria contains moderate, diffuse infiltrates of chronic inflammatory cells. The features are those of hyperkeratosis with moderate epithe-

Table 1 Types of lesions seen in 358 patients (542 lesions) grouped as suggested by the EEC-WHO. Group 1 lesions strongly associated with HIV, Group 2 lesions less commonly associated with HIV and Group 3 lesions seen in HIV infections

Lesion	Group 1 (%)		Group 2 (%)		Group 3 (%)	
Candida total	105	(19)				
Pseudomemebranous	35					
Erythematous	32					
Hyperplastic	20					
Angular cheilitis and mixed	18					
Oral hairy leukoplakia	77	(14)				
Kaposi's sarcoma	34	(6)				
Non Hodgkin's lymphoma	4	(0.7)				
Periodontal disease	24	(4.4)				
Necrotising stomatitis			1	(0.18)		
Xerostomia			19	(3.5)		
Enlarged salivary glands			10	(1.8)		
Non specific ulceration			52	(9.6)		
Herpes simplex			13	(2.3)		
Human papilloma virus			80	(14.8)		
Epithelioid angiomatosis					1	(0.18)
Leishmaniasis					1	(0.18)
Recurrent aphthous stomatitis					38	(7.0)
Cytomegalovirus					7	(1.3)
Erythema multiforme					2	(0.4)

Not all the lesions are quoted here, as there were some not considered to be related to HIV infection (see text). In this table, those lesions termed 'human papilloma virus' are included on the basis of their clinical appearance and behavior, not as identified by PCR.

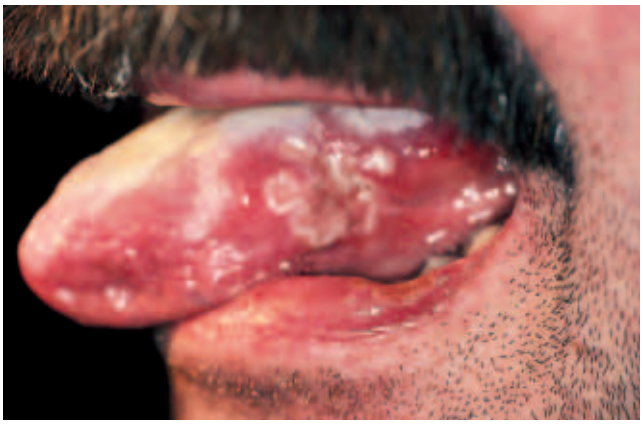

Fig 2 CMV Ulcer lateral tongue

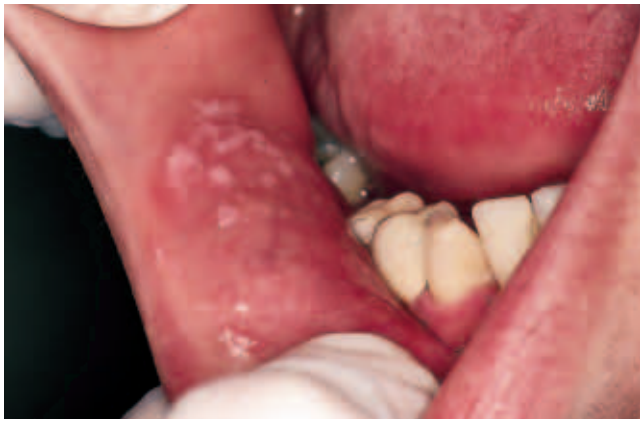

Fig 3 Papillomata

lial dysplasia'. See Fig 4 as an example of a dysplastic viral lesion.

The warts varied in appearance from the typical papilliferous appearance, to fairly flat, pale multiple lesions, as shown in Fig 3. The warts were found in all parts of the mouth with the lips being the most frequent site. Warts were numerous in both intra- and extra-oral sites, which were sites subjected to

friction e.g. tooth brushing, cheek biting. Many were disfiguring and evolved over, and persisted for months, severely affecting the patient's quality of life. Of the patients with warts 24 (30%) were on triple therapy. Of the 39 patients on triple therapy 24 (61%) had warts, 7 (18%) had ulcers and 8 (20%) had neither of these conditions.

Table 1 gives the number of lesions seen in the three categories specified by the EEC-WHO definitions of lesions associated with HIV infection, including some of the rare conditions such as epithelioid angiomatosis (Speight et al, 1991) and leishmaniasis (Chaudhry et al, 1999). The lymphomas presented in several ways: ulceration and gingival and periodontal lesions in different parts of the mouth. Additional diagnoses, not contained within the HIV related conditions, included 14 dental problems, 11 white patches with mild dysplasia, 8 traumatic lesions, 7 mucocoeles, 18 patients with non-dental pain or halitosis, 5 patients with benign oral lesions and one patient with lichen planus.

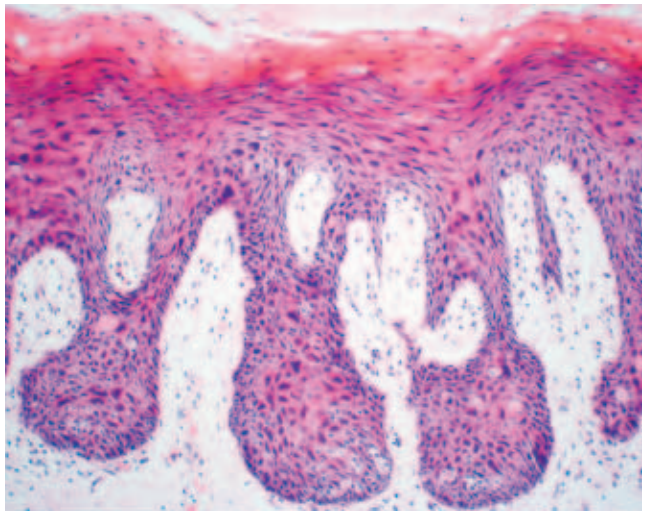

Fig 4 Histological appearance of dysplastic viral wart. Viral wart mucosa demonstrating bulbous rete peg pattern and epithelial cell nuclear hyperchromatism and pleomorphism and vacuolisation consistent with viral infection.

DISCUSSION

Over 60% of patients with HIV/AIDS prior to the introduction of HAART would at some stage have an oral lesion related to HIV/AIDS, but this has been shown to have dropped to 40% following the introduction of HAART (Robinson et al, 1996). This cross-sectional study over a nine year period shows a change in the oral manifestations of HIV over this period, some of which may be due to the introduction of HAART which resulted in raised CD4 counts and a better functioning immune system.

This is the largest and only series of UK HIV/AIDS patients examined by one individual specialist in oral medicine using the clearly defined EEC/WHO criteria (1991, 1993) over a nine year period. The data was collected prospectively and includes every single patient referred to the oral medicine clinic. In terms of global figures, the number of patients in this series is low which makes correlations difficult. Data from the dental clinic within this department included 2789 dental examinations, and these did show that oral lesions were affected by the introduction of HAART (Greenwood et al, 2002). The last conference on oral manifestations of AIDS held a workshop to look at the prognostic value of oral lesions and to examine any reasons for the changing incidence of lesions. The workshop found considerable variation in the data and suggested that not just drug therapy but HIV virus type may be responsible for the changes. It also highlighted the need for developed countries to work alongside the developing ones to help ascertain the pattern of lesions (Birnbaum et al, 2002). Not all the data is available for all the patients as some came from outside of the department and not all of these patients knew their data. The study population is primarily homosexual men and so it is possible that their sexual practices could predispose them to certain lesions, which may not be typical of all patient groups with HIV/AIDS. A review of lesions found in HIV/AIDS patients shows extreme variations (Pinheiro et al, 2002), so it is not helpful to compare our data with others.

The range, type and manifestations of oral ulcers from this series have been previously described (Zakrzewska et al, 1997), and in this larger series it can be seen that drug therapy, and therefore probably raised CD4 count, results in fewer episodes of large non-specific ulcers. Oral ulceration has an acute and painful presentation, but responds well to medications, such as thalidomide. This is in contrast to the relatively painless, but long lasting presentation of oral warts. A higher percentage of patients had warts (30%) than oral ulcers (6%) when they were on triple therapy.

The increased numbers of patients with papillomata and condylomata have increased and Green-

span et al, (2001) have shown that they may be related to HAART. In our small series we found no correlation. An important feature however is that 44.2% of biopsied wart lesions show dysplastic change. It would seem probable that these patients could go on to develop squamous carcinomas especially as many of this cohort of patient smoked cigarettes. Work in similarly immunocompromised renal transplant patients has shown an increased incidence in the development of squamous carcinomas of the lip over many years (King et al, 1995). A preliminary study examining the viral wart biopsy material from the patients in this study has suggested there may not be a great risk of developing oral squamous carcinoma (Sancheng et al, 2002). Human papilloma virus (HPV) typing may be important to identify patients at greater risk, as has been shown in the case of cervical carcinoma (WHO, 1995). There is case report of a patient with a warty carcinoma of the cheek that was found to have HPV 16 and 18 in the koilocytic cells (Piattelli et al, 2001). There are also a considerable number of studies being carried out to look at the relationship of HIV, HPV, malignancy and dysplasia not only in the mouth but also in cervical and anal areas (Hillet et al, 2002; de Sanjose and Palefsky, 2002). This is an area of current research and surveillance that is required to see if oral squamous carcinoma is more likely to occur in HIV/AIDS patients who are also infected with HPV, especially HPV 16 and 18. For the patients themselves there is the uncertainty of infectivity and a dilemma over whether sexual practice needs to be changed in the light of this.

This data validates the inclusion of those conditions listed in group 1 of the EEC-WHO definition, as lesions strongly associated with HIV. In addition, when this UK data is placed into the EEC-WHO groups 2 and 3 (as shown in table 1) the increased incidence of non-specific ulceration, HPV and CMV lesions suggest that they are strongly linked to an HIV diagnosis and should be moved to a higher group. These diagnoses appear to have high specificity and sensitivity whereas enlarged salivary gland and herpes simplex do not have such high specificity and sensitivity for HIV and therefore should remain in group 2.

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