INCIDENCE AND PROGNOSTIC VALUE OF ORAL CANDIDIASIS IN HIV INFECTION

Cristina POPA, Carmen STELEA, Eugenia POPESCU
"Grigore T. Popa" Iasi University of Medicine and Pharmacy Iasi, Romania
Department of Oral and Maxilo-Facial Surgery

INCIDENCE AND PROGNOSTIC VALUE OF ORAL CANDIDIASIS IN HIV INFECTION **(Abstract):** Oral candidiasis is the most frequent lesion encountered in HIV infected patients and is detected before any other clinic symptoms of oral pathology. Its growth is a complex process of changes in the oral cavity, and sometimes disorders involving the entire body. Its risk is increased by serious factors as follows: autoimmune deficiencies (illness of the primary cells which acts as modulators of the immune response), xerostomia, malignant neoplasm, different therapies (chemotherapy, antibiotic therapy, therapy with steroids) or iron deficiency anaemia.

Keywords: oral candidiasis, HIV infection, prognostic value

INTRODUCTION

The oro-maxilo-cervico-facial territories are areas where manifestations of HIV infection are most often observed. The vast majority of infected patients present at least one oral lesion, which sometimes can be the only expression of the disease. In this context, it is very important for dentists to be well informed of the oral signs of HIV infection. Affection of the oral mucosa is constant, appears early in the disease and it is a clinical indicator of the prognosis, which usually indicates an ominous evolution. Oral candidiasis, frequently observed in HIV infected patients, appears almost always before other clinical oral manifestations. It represents an indicator of imunosuppression, but it can also imply an increase in viral load associated with AIDS or resistance to anti-retroviral medication. The development of candidiasis is a complex process which is influenced by changes that may take place in the oral cavity; sometimes it implies disorders involving the entire body. Increased risk of developing oral candidiasis is associated with several factors including: established imunosuppression (disease of the primary cells implicated in modulation of the immune response), xerostomia, malignant tumours and therapy (chemotherapy, antibiotherapy, steroid therapy) or iron deficiency anaemia.

MATERIAL AND METHODS

Our study covers a period of 6 years and analyses a number of 117 patients diagnosed with HIV infection or AIDS associated with various oral pathology. The study aims to identify characteristics related to the incidence of the disease and biological, clinical and therapeutic aspects which could offer information towards the overall prognosis, therapeutic response and evolution of the disease.

Over the period of study, we followed:

- particularities of the patient group studied, analysis of the early clinical symptoms, the

correlation to the disease stage with reference to specific oral symptomatollogy.
- the relation between specific clinical and haemato-immunological particularities in different forms and stages of the disease.
- the identification of clinical and therapeutic factors with prognostic value in a unitary analysis of the evolution and response to therapy.

Patients considered eligible for the study:
- serological diagnosis (ELISA confirmed WESTERN-BLOT) was infection with HIV
- absence of history and/or clinical signs of oral, oesophageal candidiasis and absence of anti-fungal treatment at least 3 months prior to present examination.
- with oral pathology encompassing HIV infection

Patients excluded from the study:
- HIV infection without associated oral pathology
- which were associated with other immunological and/or haematological pathology
- with high risk of death.

Evaluation of initial diagnosis was followed by compulsory complete anamnesis, motives for presentation, complete objective clinical examinations, and biological and imagistic paraclinical examinations. Immunological markers (total lymphocyte and beta 2 micro-globulin) or viral markers (HIV p24 core antigen) were also used to monitor HIV infection and response to antiretroviral therapy.

The associated oral pathology was monitored by an examination of all patients keeping in line with strict clinical protocols of classification and identification of diagnostic criteria for oral lesions based on recommendations of "EC-Clearinghouse on Oral Problems Related to HIV Infection and WHO Collaborating Centre on Oral Manifestations of the Immunodeficiency Virus".

RESULTS

From the total number of patients studied (117 HIV infected), 71 presented signs of low grade or moderate disease (stage A and B-table I), while 46 were classified in final stage of HIV infection (AIDS) (fig. 1).

Table I

Clinical category	Nr. of cases
A1	5
A2	0
A3	10
B1	37
B2	5
B3	14
C1	23
C2	16
C3	7

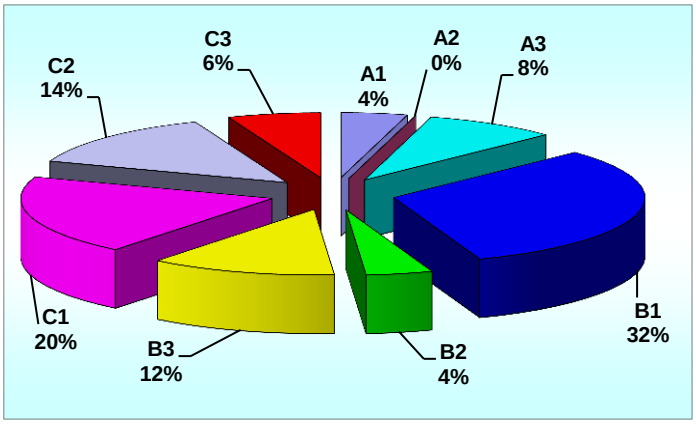

Figure 1. Retrospective quantification of the patients on the first apointment

A number of 18 patients were diagnosed as HIV positive on presentation in the out-patient department for various oral affections (5 of whom were in final stage AIDS) (fig.2).

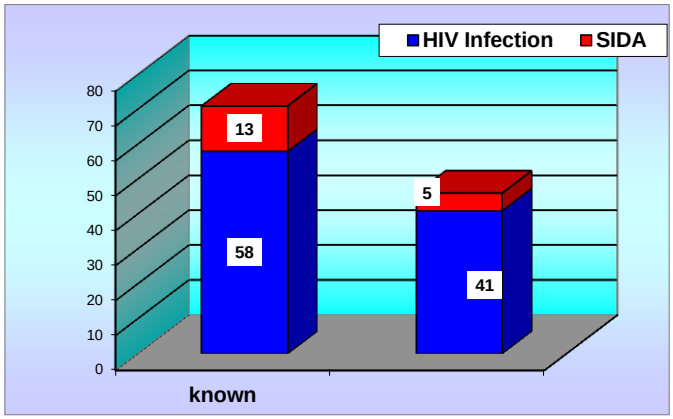

Figure 2. HIV infection known or detected in clinic

Oropharyngian candidiasis was the most frequent lesion found in HIV infected patients. The diagnosis (isolated or recurrent) was made in a number of 88 patients (75,2%). Systemic candidiasis (Candidemia) and fungemia was found in one single patient only.

In approximately 50% of the cases (over a median of 3-5 years) one or several episodes of oral candidiasis were observed. The presence of oral fungal lesions represented the early symptoms that lead to initial diagnosis of AIDS. Although it is not a pathognomic symptom, oral candidiasis, especially in chronic variation, multifocality, or when associated with esophagian candidiasis, was suggestive of AIDS diagnosis, with completion of the clinical pattern developing in the following months.

The following anatomic-clinical forms of candidiasis were encountered: erythematous, pseudomembranous, hyperplasic and angular cheilitis. Table II and fig. 3 present the incidence of cases with candidiasis:

Table II. Incidence and forms of oral candidiasis reported in the investigated patients

Erythematous Candidiasis (atrophic)	16
Angular cheilitis	21
Pseudomembranous Candidiasis	38
Chronic hyperplasic Candidiasis	13

Patient inclusion criteria followed CDC 1994 protocols, with the mention that once a patient was classified as being HIV positive, he can no longer be reclassified in any other clinic-immunological category, even if his clinical or immunological status is modified.

Prevalence of oral candidiasis depended on the clinical stage of the patient as follows:

- stage I (without immunosuppression) – predominantly angular cheilitis registered in 19,4% of the cases
- stage II (moderate suppression) – predominantly erythematous candidiasis - 30,4% of the patients
- stage III (severe imunosuppression) – predominantly pseudomembranous form - 77%

patients (fig.4).

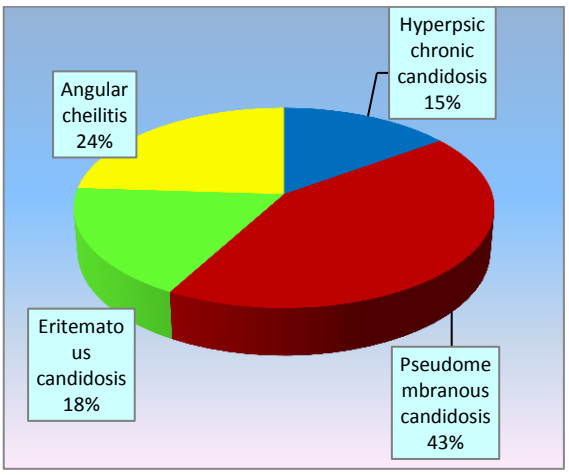

Figure 3. The incidence of the cases and forms of oral candidosis reported

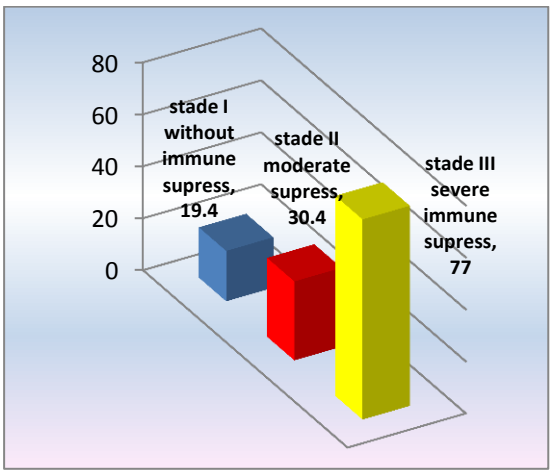

Figure 4. Oral candidosis: clinical forms prevalences correlated with the immune status

Table III presents the relation between the immune status and oral candidiasis in 84 patients (immunological status was monitored over a period of +/- 3 months after initial diagnosis was made).

Table III.

Oral mucosa	LyT CD4/mmc	LyT CD8/mmc	CD4/ CD8
Normal mucous (24 cases)	540	1100	0,50
Erythematous candidiasis (40 cases)	320	790	0,40
Pseudomembranous candidiasis (20 cases)	220	840	0,26

1*) Acute erythematous candidiasis (atrophic)*

All patients presented a mild sensation of discomfort or burning; in 20 cases it was not reported as subjective complaints. The lesions presented in the form of an erythematous area (with varying colour intensity), having a preference to appear at the palate or dorsal part of the tongue. Occasionally, lesion of the tongue and the internal aspect of the lips were covered with a fine white-creamy non-adherent film.

Considering all these aspects the clinician should carefully examine the oral mucosa of the infected patient in order to diagnose and treat different forms of oral candidiasis, starting in the early stages when possible. In 28 cases, erythematous candidiasis preceded the pseudomembranous form. Diagnosis was confirmed in 15 cases, by the presence of *Candida spp* in cultures with Saburaund media; another criterion was positive response to antimicotic treatment.

The clinical form described in literature „median rhomboid glossitis" was observed in 7 cases, as an area of soft, red depapilation, followed by transformation into a rusty, lobulated induration. Form and dimensions varied, but the most frequently encountered was an area of well demarked, 1/1, 25 cm oval or rhomboid shaped lesion on the posterior 1/3 and dorsal aspect of the tongue.

2) Pseudomembranous Candidiasis

Subjectively, patients complained of dry mouth, burning sensation, dysphagia and hyper-salivation. Other complaints included pain, sensation of tension in the affected mucosa, and altered gustation. Clinical examination showed the presence of papules or yellowish/white plaques (of a creamy consistency, non-adherent and easily removed by minimal pressure), covering the erythematous surface as an isolated or multifocal layer. Petechial or isolated erythematous puntiform elements were observed occasionally after debridgement of the white deposits. In general, the localisation of these lesions did not present a tropism towards a specific area of the oropharynx (oral mucosa, in the oropharynx, margins of the ventral aspect of the tongue, palatine mucosa).

Some of the lesions had a sudden debut (acute pseudomembranous candidiasis), usually after antibiotherapy; others had a slow, delayed evolution (chronic pseudomembranous candidiasis) which was observed in the majority of HIV positive patients.

Current diagnostic criteria include clinical aspect and positive response to anti-fungal therapy. Histological examination was possible only in a limited number of cases (35 patients). Microscopic examination, with Gram staining, showed the presence of fungi (pseudohypha, spores) in pseudomembranous deposits made up from desquamated keratinocytes, keratin, inflammatory cells, bacteria and fibrin. Biopsy examination revealed a hyperplasic epithelium, inflamed, infiltrated with polynuclear neutrophils, fungal hypha penetrating epithelial basal cells from the surface inwards deeply. In the lamina propria, a lymphoplasmocytic infiltrate was found. In specific stains - H-E, PAS and silver impregnation, fungal hyphae were remarked, with typical „bamboo stick" aspect. From the 98, oral gavaj before and after antimicotic treatment, from the 35 patients, the following biotypes of Candida were isolated:*C. albicans (*66%*), C. krusei (*12%), *C. torulopsis glabrata (*16, 5%), *C. tropicalis (*4%) and *Geotrichum candidum (*1, 5%).

C. albicans was isolated in over 75% of the patients after treatment with ketoconazol. In 10 patients with recurrent oral candidiasis, several biotypes were isolated.

There was no correlation observed between the different biotypes of *C. albicans* and the clinical picture of the oral lesions, stages of HIV infection or the number of CD4 cells. In reference to the different biotypes identified between different episodes, a conclusion could not be drawn as to the reappearance of the lesion as an effect of exogenous reinfection or relapse (through modification of the same stem).

Data obtained from literature reports the last possibility without having justified the pathogenic mechanism; alternation of the different biotypes could be in fact a different phenotype expression of the same fungal genotype. These phenotype variations could possibly be due to modifications in the local immune response, physiochemical variations induced by therapy or even ecological oral variations. The differential diagnosis was made with all possible white lesions of the oral mucosa.

3) Chronic Hyperplasic Candidiasis

Also named *Candida* leukolpakia,it is the rarest form and also the most controversial. Some authors consider it as being a candidiasis superimposed over a pre-existing leucoplasic plaque, but it has been demonstrated that a fungus can on its own induce hyperplasic lesions at the level of the oral mucosa.

It was represented in 5 patients under the form of a plaque with variable thickness, an

irregular aspect, surrounded by an erythematous area, situated on the dorsal surface of the tongue or on the superior or inferior labial mucosa. Their removal by debridgement was not possible, persisting up to 1-2 years. In 3 patients this was associated with angular cheilitis.In 12 patients, multiple Candida lesions were discovered as being *chronic multifocal candidiasis.*In one case, the leucoplasic area was in intimate contact with zones of red colouring, constituting *spotted leucoplasia*, a situation where it was clinically differentiated from erythroleucoplasia, and which, from the microscopic point of view, presented frequent displasic lesions. The diagnosis was confirmed microscopically, demonstrating fungal hypha infiltrating epithelial hyperplasia and also by therapeutic tests- complete resolution under antifungal treatment.

4) Angular cheilitis

Subjective symptoms frequently encountered were sensation of dryness and burning at the level of the lips, associated with impossibility to consume hot or spiced foodstuff.

It has been described under the form of an erythematous area, fissured and covered by crusts, situated at the level of the labial commisures. The surrounding tissue is sheared. The majority of the patients have bilateral lesions, training discomfort and pain on opening the mouth, thus limiting normal oral function.Diagnosis is confirmed by presence of fungus (hypha and blastosporea) from oral prelevations and favourable results to antifungal therapy.

In the study group were isolated *C. albicans* (20% of cases), or associated with *Staphylococcus aureus* (60% of cases), while the rest 20% had just *Staphylococcus aureus.* Pathogenesis of the affection is not sufficiently known and is probably due to the frequent damping of the labial mucosa (due to xerostomia) which permits the micro-organism access to superficial plans of the labial epithelium, accompanied by their desquamation.

In the majority of the patients, the process of localized inflammation at the labial commisures was associated with atrophic or membranous candidiasis, with different localizations.

In the absence of suggestive lesions, and in conditions of suspected candidiasis, the use of quantitative culture from undiluted saliva or from oral gavaj was implemented

DISCUSSIONS

Oral Candidiasis is one of the clinical indicators of the development and progression of infection with the human immunodeficiency virus. The development of this pathology, without a local cause (xerostomia, antibiotherapy, corticotherapy) has to suggest an HIV infection. Our research has proven a close correlation between oral candidiasis after T lymphocyte depletion, with the report of CD4/CD8 and with laboratory and clinical markers of HIV progression.The study has proven that the presence of oral lesions has been in close concordance with the value of biological test results (absolute number of lymphocytes, beta 2 microglobulin, IgA). This correlation (even in the absence of determining CD4 lymphocytes) has imposed an attitude of prophylaxis of HIV infection in asymptomatic patients, with modified biological tests only.Atrophic Candidiasis precedes the pseudomembranous form in the case of HIV infection and appears early in the disease. No significant statistical correlations were found between the presence of atrophic candidiasis and the low CD4 count ($p=0, 68$) or AIDS ($p=0, 81$). The pseudomembranous form is most frequently encountered in patients with AIDS and had a significant statistical association with CD4 lymphocyte count

under 200 cells/mm3, appearing frequently in the final stages B3, C1, 2, 3 of HIV infection. Angular cheilitis constitutes a candidic associated manifestation of HIV infection which, in our study, demonstrates a severe immunodeficiency.Keeping in mind the possibility of an asymptomatic evolution of candidiasis, the clinician should carefully examine the oral mucosa of the infected patient and thus be able to diagnose and treat the different forms of candidiasis in its early stages. Patients without oral candidiasis have had a better prognosis as compared to those with clinical forms of candidiasis. Thus we have established the prognostic value of oral manifestations of candidiasis, as a marker of evolution in AIDS. Esophageal candidiasis appeared later, in a case with advanced immune deficiency representing a criterion for diagnosing AIDS (over 20% of cases). There were no observations made between AIDS related deaths for different types of oral candidiasis.

CONCLUSIONS

Oral manifestations should be considered as clinical signs of HIV infection and as an objective indicator of disease progression. In this context, oral candidiasis is one of the early clinical indicators of infection and its severity. The pseudomembranous form and the atrophic form of candidiasis are markers of HIV, highly predictive for the further development of AIDS.

Oropharyngian candidiasis has been associated with other markers of prognosis: reduction of CD4 lymphocytes, therapy with anti-retroviral agents and evolution of the disease AIDS. Furthermore, for patients with AIDS, oral candidiasis has been a pre-monitor marker for esophageal candidiasis.

The ability to recognise the predictors of HIV progression may step up the decision in administration of early protection for HIV infected individuals. Dentists can play an important role in the detection of symptoms associated with HIV/AIDS and can considerably improve the quality of life for these patients.

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