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RESEARCH ARTICLE

CONTRIBUTION OF THE MYCOLOGY LABORATORY IN THE MANAGEMENT OF ORAL CANDIDOSIS IN IMMUNODEPRESSED PATIENTS

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Abstract

The authors report a series of 49 cases of oral candidiasis including 20 symptomatic, listed on 100 immunocompromised patients collected at the Mohammed V Military Hospital in Rabat over a 12-month period. The objective of this work was to define the risk factors that lay the foundation for fungal proliferation in the mouth, through early detection in asymptomatic or non-asymptomatic patients. Mycological analysis in the laboratory was based on direct examination and culture on Sabouraud chloramphenicol medium with and without cycloheximide, then identification of the fungal species by API 20 C AUX galleries and the VITEK 2 compact® . The prevalence of oral candidiasis was 49%. The mean age of the patients was 54 years with a sex ratio M / F of 1.04. The contributing factors identified were hyposialia (p = 0.0337), corticosteroid therapy (p = 0.025 and dental removable prostheses (p = 0.000791). The fungal species identified were *Candida albicans* (79%), *Candida dubliniensis* (7%), *Candida ciferrii* (4%), *Candida famata* (4%), *Candida glabrata* (4%) and *Candida lusitaniae* (2%).

Conclusion: The oral localization of candidiasis remains very frequent in immunocompromised subjects. Their treatment involves first of all the search for contributing factors and early detection in the presence of asymptomatic forms that only mycological analysis can identify the variety.

Introduction:-

The oropharyngeal localization of candidiasis is well known to all, in fact these microorganisms are often saprophytes which become pathogenic each time the patient's immune situation becomes compromised, most often due to an imbalance of the bacterial flora of medicinal origin; but also due to certain therapeutic prescriptions for various pathologies of a tumor nature or acquired or constitutional immunosuppressions, prolonged corticosteroid therapy, radiotherapy or chemotherapy. The terrain is also an important factor in the pathogenicity of these mycosis, mainly Candida albicans [1], but also and more rarely “non albicans” which can be identified using molecular biology and genetics techniques [2, 3].

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The aim of our work was to analyze the risk factors at the origin of the pathogenicity of oral candidiasis infections by collecting epidemiological elements relating to age, sex, terrain, and diseases causing a disease immunosuppression favorable to their emergence and multiplication. The interest of the examination by the clinician remains capital in the early detection, the contribution of the data of the laboratory remains capital for the identification of the candidate and its prototype by the direct examination, the culture and as well as in the therapeutic orientation after carrying out an antifongigram. The treatment remains in continuous evolution due to the varied therapeutic regimens adapted to the age, the field and the type of the identified candida.

Materials and Methodology:

The sampling technique is simple by swabbing the oral mucosa with a sterile swab adressed in a sterile tube to the Mycology department where a direct examination and cultivation will be carried out. This direct examination allows the fungus to be identified and visualize its abundance**.** It is carried out in the fresh state, after trituration of the swab on a drop of physiological water spread on a slide which will then be covered with a coverslip for the study under an optical microscope with an objective x 40. The fungus are thus visualized in the form of small rounded or oval cells of 2 to 4 µm, with thin walls and budding more or less accompanied by pseudo-filaments.

The Culture is done on a selective medium, and if the Candida are not very demanding and easily grow on Sabouraud's medium (fig 1), it is not the same if the sample is polymicrobial where it will be necessary to carry out a specific fungal research and seeding on a field impregnated with antibiotics, often chloramphenicol with or without cycloheximide. White, creamy, thick and shiny colonies are usually seen after incubation in 24 to 48 hours at 37C ° (fig 1, 2).

Figure 1:- Incubation in an oven at 37 ° C for 48 hours. Reading takes place at 24 and 48 hours.

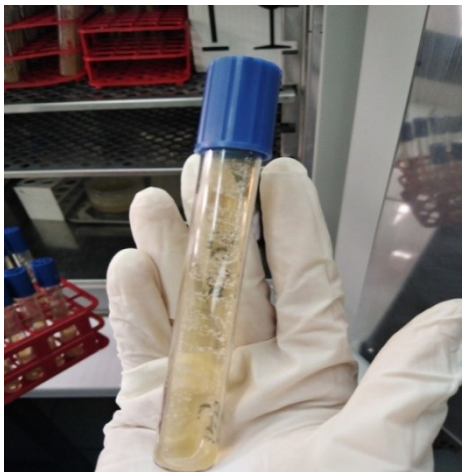

Figure 2:- Positive culture

Candida can thus be identified using API 20 C AUX galleries and antifongigram by the VITEK® 2 compact.
API 20 C AUX is a system for the precise identification of the most frequently encountered yeasts.The gallery of 20 wells (Fig 3) allows 19 tests to be carried out for the assimilation of sugars. The wells are inoculated with a semi-agar medium and the reading is done by comparison with growth controls and the identification obtained using the analytical catalog or identification software.

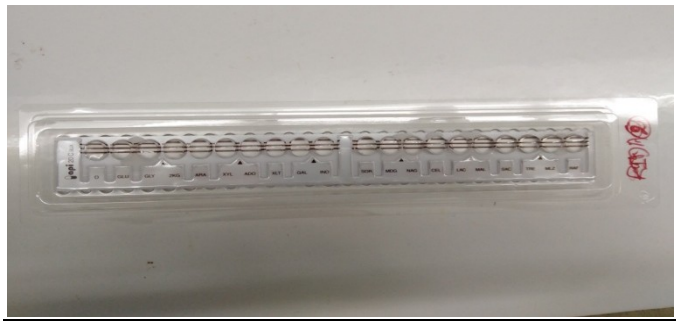

Figure 3:- API 20C Aux gallery.

Figure 4:- The VITEK® 2 compact .

As for the antifongigram, it is produced by the VITEK® 2 Compact (Fig.4), standardized and fast, giving results within 13 hours.

Statistical analysis of the data is carried out by the software R. using the Student test for the quantitative variables and the Chi-square test for the qualitative variables. The risk of error has been set at 5%. The relative risk (RR) and the 95% confidence interval (95% CI) were calculated to determine the importance of the association with the risk factors.

The results are statistically significant if p: 0.05.

Results:-

100 oral samples were taken from 100 patients whose mean age was 54.9 years (range: 20 - 92 years), 29% of patients were between 50 and 60 years old, the sex ratio was 1.27H / F. 99% of the patients were in acquired immunosuppression.

Diabetes was noted in 37% of patients, tumor pathology was present in 38% of cases, and infection with the Human Immunodeficiency Virus HIV was found in 6% of cases.

Other favorable pathologies have been identified, hypothyroidism in 5% of cases, cirrhosis (6%), anemia (7%), autoimmune diseases (28%), and cardiovascular diseases (25%).

31% of patients were on chemotherapy and 14% had received radiotherapy sessions.

14% of patients were on antibiotic therapy for various pathologies, corticosteroid therapy was found in 21% of cases and immunosuppressants in 17% of patients. Toxic habits were noted in 18% of cases and alcoholism in 3% of patients.

Particular attention was given to the analysis of oral hygiene which was very insufficient in 97% of cases, and the wearing of removable denture all in resin was noted in 30% of situations. Hyposialia, for its part, was present in 48% of patients.

Of the 100 oral samples, 49 cultures were positive (49%) in 24 women (48.97%) and 25 men (51.02%). A sex ratio M / F equal to 1.04, their mean age was age 54 (range 20-92).

The mycological study made it possible to isolate the following types:
Candida albicans: 40 cases (79%), *Candida dubliniensis* 3 cases (7%), *Candida glabrata* 2 cases (4%), *Candida famata* 2 cases (4%), *Candida ciferrii* 2 cases (4%) and *Candida lusitaniae* 1 case (2 %) (fig 5),*Geotrichum Capitatum* was noted in 2% of cases (fig .6)

Figure 5:- Candida sp: Macroscopic appearance on Sabouraud agar.

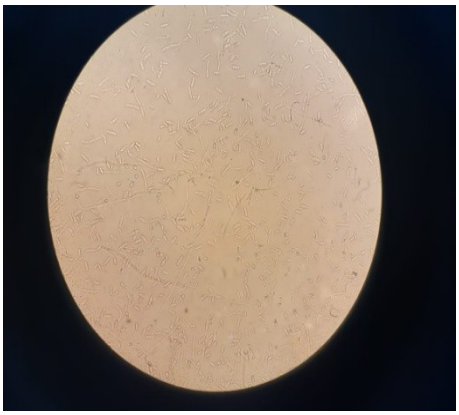

Figure 6:- Microscopic appearance of *Geotrichum* sp.

The clinical presentation of oral candidiasis was varied, we found a thrush in 10 cases (20%), stomatitis under denture in 3 cases (6%), stripped tongue in 3 cases (6%), perlèche in 2 cases (4%), chronic pseudomembranosa in one case (2%), black villous tongue in one case (2%), pain or burning sensation in 12 cases (24%), and dry mouth sensation in 16 cases (32%).

Discussion:-

The correlation between clinical and mycological examinations has always been the subject of controversy. in our series among of the 49 patients with oral candidiasis confirmed by mycological examination, only 20 presented clinically apparent lesions.

Comparative analysis of the population with and without oral candidiasis did not reveal the implication of gender ($p = 0.915$) and age ($p = 0.150$).

On the other hand, the involvement of other factors was retained, and in particular corticosteroid therapy ($p = 0.025$), the wearing of dental prostheses ($p = 0.000791$) and hyposialia ($p = 0.0337$).

These data enabled us to compare our results with those reported in the literature and to deduce the consequences regarding the factors favoring the emergence and colonization of the mouth by yeasts, as well as the mechanism of their pathogenesis.

In fact, the prevalence of colonization by Candida is 20 to 75% in healthy subjects, 47% (13-76%) in hospitalized subjects [4, 5], and varies according to the location, the population studied and the sampling techniques used.

The pathogenicity of the yeasts begins with the mucous invasion, facilitated by a debilitated terrain, such as broad spectrum antibiotic therapy, immunosuppression by corticosteroid therapy, neutropenia linked to immunosuppressive treatment, diabetes, HIV. The infection is frequently linked to the *Candida albicans* and more rarely to *C. krusei* and *C. glabrata* [6].

According to several publications, age does not seem to be a contributing factor, this was the case in our series with $p = 0.150$ [7,8]. The existence of data reporting opposite results seems to be linked more to the condition of elderly subjects, of course, but the latter are most often carriers of dental prostheses and polymedicated [7-9].

It is the same for gender, the majority of writings report the absence of difference between the sexes of males and females, the immunosuppressive effect of estrogen and progesterone being raised according to other studies [10, 11].

Concerning yeast species, *C. albicans* is most frequently found, mainly in the digestive and genital tracts in 10 to 20% of healthy adults [12], followed by other types *(C. glabrata* and *C. tropicalis*,*C. krusei*, *C. famata*, *C. lusitaniae*, *C. guilliermondii* and *C. dubliniensis*) rare in healthy subjects.

In our study, *C. albicans* was the most isolated, found in 79% of positive cultures.

The other types of "non albicans" Candida are found in varying proportions, in particular *C. dubliniensis* isolated in 3 cases (7%), *Candida glabrata* (4%), *Candida famata* (4%), *Candida ciferrii* (4%) and *Candida lusitaniae* (2%).

Concerning the risk factors often incriminated, they must be researched. Diabetes remains the most common ground, and the exact mechanism of etiopathogeny in mycotic growth seems not yet very clear. This would be an increase in the concentration of salivary glucose which would increase the number of receptors for Candida [13]. However, the prevalence of oral candidiasis does not seem to be significantly increased compared to healthy subjects by studying the data in the literature [14, 15].

For tumor pathologies and their treatment (chemotherapy and radiotherapy), they generate significant immunosuppression. Several tissue abnormalities are found with oral ulcerations and hyposialia linked to the imbalance of the oral flora [16]. Colonization is noted in 50% of oral infections in patients undergoing anti-leukemic chemotherapy and in 60% of patients treated with antineoplastic chemotherapy for solid cancers [17].

In patients with Human Immunodeficiency Virus (HIV), oral candidiasis is the most common opportunistic involvement both during the early phase of infection and after seroconversion. These are often progressive, relapsing forms [18], favored by the decrease in CD4 + T lymphocytes associated with a high viral load in untreated patients.

On another aspect, certain drug treatments, because of their action on the immune system, can promote the emergence of infection by fungi, this is the case with prolonged antibiotic therapy and immunosuppressive

treatments. Indeed, the latter generate a weakening of the body's immune defenses, mainly linked to a drop in the number and activity of immunity cells [6]. As for broad-spectrum antibiotics, they are at the origin of a disturbance of the biological balance of the usual saprophytic flora of the mouth in favor of the proliferation of pathogenic yeasts. This seems to be linked to the muramic acid released from the killed bacterial wall, which would promote the filamentation of Candida and increase its virulence [19].

Other local factors remain important to consider in the pathogenesis of oral candidiasis infection, tobacco represents an element likely to increase its prevalence, as well as the wearing of removable prostheses [20, 21]. Tobacco acts by chemical attack on the epithelial tissue facilitating candidiasis colonization [22] favored by nutritional factors such as nicotine, nitroso-diethylene amine and aromatic hydrocarbons.

As for dental prostheses, 38% of patients who are carriers' present oropharyngeal candidiasis and the samples are positive from the dentures in 93% of cases.

In our study, out of 30 patients with prostheses, 21 were carriers of oral candidiasis with a $p = 0.00079$.

The salivary flow being modified quantitatively and qualitatively, as well as the prosthetic acidosis this disrupts the mechanical self-cleaning effect [23].

Therapeutically, the treatment of oral candidiasis begins with the identification and treatment of local and general risk factors. Several antifungal molecules are known and the indication of their choice depends on several factors including the terrain, the type of candidate and the data of the antifongigram.

In patients without immune deficiency, local treatments (Nystatin, amphotericin B, miconazole) are favored, and the use of adjuvants is recommended. In children and infants, Fungizone and Daktarin seem favorable [24].

As for systemic treatment, it should be reserved for recurrent forms and in patients with patients with a history of systemic mycosis to reduce the risk of developing resistance [25]

For the immunocompromised patient, local treatment should be prescribed based on fluconazole or itraconazole in solution [30]

Conclusion:-

The buccal localization of candidiasis remains very frequent in immunocompromised patient. Their treatment involves first of all the search for contributing factors and early detection in the presence of asymptomatic forms that only mycological analysis can identify the variety.

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