Original Paper

Histopathological Study of Oral Pseudoepitheliomatous Hyperplasia

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ABSTRACT: Pseudoepitheliomatous hyperplasia, also called Heck's disease, is an epithelial, inconstant and conjunctive proliferation that develops as a response to a great variety of stimuli. It is a lesion associated to different diseases, being found in the following etiopathogenic conditions: infectious pathogenic conditions, tumoral pathogenic conditions, inflammatory pathogenic conditions. We studied oral pseudoepitheliomatous hyperplasia for which we performed a histopathological study, on a group of 47 cases of oral pseudoepitheliomatous hyperplasias, where we investigated the following: oral epithelium changes, changes in the underlying lamina propria and associated etiopathogenic conditions. The main changes of the oral epithelium were: elongation of the epithelial apexes (17.02%), acanthosis (100%), dyskeratosis (14.89%), and in the underlying lamina propria: fibrosis (29.78%), inflammatory infiltrate (70.21%) and vascular proliferation (10.64%). The most frequent associated etiopathogenic conditions were the infectious ones (55.31%), followed by the tumoral ones (29.79%), on the last place being the inflammatory conditions (14.89%).

KEYWORDS: *pseudoepitheliomatous hyperplasia, histopathological study, epithelium, etiopathogenic conditions*

Introduction

Pseudoepitheliomatous hyperplasia, or Heck's disease, is an epithelial, and less an inconstant and conjunctive, proliferation as a response to a chronic irritative stimulus, interesting the mucosa and skin surfaces. Thus, it is considered that pseudoepitheliomatous hyperplasia is an active reactive benign lesion that is characterized by the epithelium hyperplasia, under the form of "tongue-like" epithelial projections in the dermis or lamina propria, sometimes having a pseudo invasive aspect [1,2,3]. Because of this, it is quite similar to a well-differentiated oral squamous carcinoma that is difficult to differentiate most of the time. Due to this fact, there exists the need to perform a biopsy. It is developed as a response to a great variety of infectious, neoplastic, inflammatory or traumatic stimuli [2,3]. It is, thus, a lesion associated to a different pathology, being found in the following pathogenic conditions: infectious pathogenic conditions (Kokh's bacillus, actinomicetes, Candidiasis, Human Papilloma Virus), tumoral pathogenic conditions (benign and malignant), inflammatory pathogenic conditions.

Being a condition that develops secondarily to another condition, its incidence is difficult to estimate. It affects both sexes almost equally, and the age of the patients varies a lot, the specialized literature including cases aged between 11 and 80 years old.

Still, the etiopathogeny and molecular mechanisms at the basis of pseudoepitheliomatous hyperplasia etiopathogeny are not fully understood [4], but, the association of pseudoepitheliomatous hyperplasia with numerous etiopathogenic conditions suggests the involvement of various intra cellular signaling ways in the pathogeny of this lesion.

The purpose of the histopathological study on oral pseudoepitheliomatous hyperplasia was to highlight the morphological changes in the oral epithelium and the underlying lamina propria, in order to perform an accurate differential diagnosis between this lesion and other clinical entities. We also observed the etiopathogenic conditions associated with oral pseudoepitheliomatous hyperplasia.

Material and Methods

For this study, there were selected 47 cases of oral pseudoepitheliomatous hyperplasia. The patients were admitted and operated within the Oral and Maxillofacial Surgery Clinic of the Emergency County Clinical Hospital of Craiova, between 2012 and 2014. Every patient included in the study gave his/ her informed consent to participate in this research study, the entire protocol being performed in accordance to the ethic procedures. The study pieces were fixed in 10% formalin, processed according to the usual

technique of paraffin inclusion and stained with Hematoxylin-Eosin within the Laboratory of Pathological Anatomy in this hospital. The study included the following investigation criteria for oral pseudoepitheliomatous hyperplasia: oral epithelium changes (acanthosis, elongation of epithelial apexes, dyskeratosis, keratinic perles±atypias/mytoses), changes in the underlying lamina propria (inflammatory infiltrate, fibrosis) and the associated etiopathogenic conditions. The images were obtained by using the Nikon Eclipse E600 microscope and the Lucia 5 program.

Results

Morphological changes of surface epithelium (Fig.1)

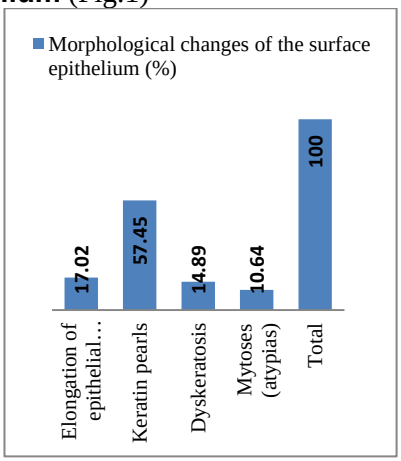

Fig.1. Morphological changes of the surface epithelium

One of the most characteristic morphological changes in pseudoepitheliomatous hyperplasia is represented by the elongation of the epithelial apexes that deeply descend into the lamina propria (Fig.2).

These changes were observed in 8 cases (17.04%). Sometimes, these apexes seem to entwine, acquiring a cribriform aspect. Another change observed in all the investigated cases was acanthosis, namely diffuse hyperplasia and thickening especially of the medial/spinous layer of the oral mucosa (Fig.3). In 27 of the investigated cases (57.44%), we also highlighted the presence of keratin pearls (epithelial pearls), most often as aggregates of keratinized spinous cells (Fig.4), and in 7 of the investigated cases (14.89%), we observed the presence of dyskeratosis as isolated cells (Fig.5). Rarely did we notice (5 cases-10.64%) the presence of mitoses and a low degree of cellular/ nuclear atypia.

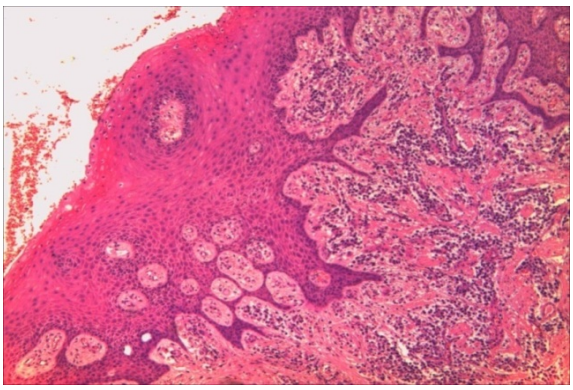

Fig.2. Pseudoepitheliomatous hyperplasia- Elongated epithelial apexes. HE staining x40

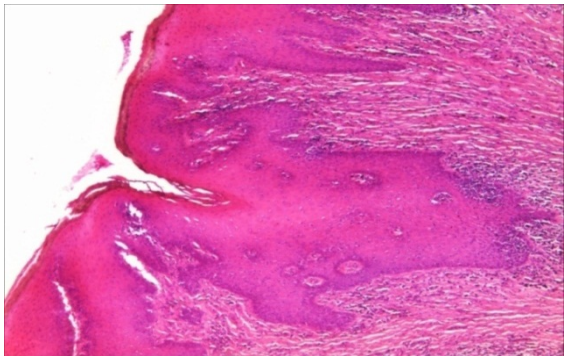

Fig.3. Pseudoepitheliomatous hyperplasia- covering epithelium acanthosis. HE staining x40

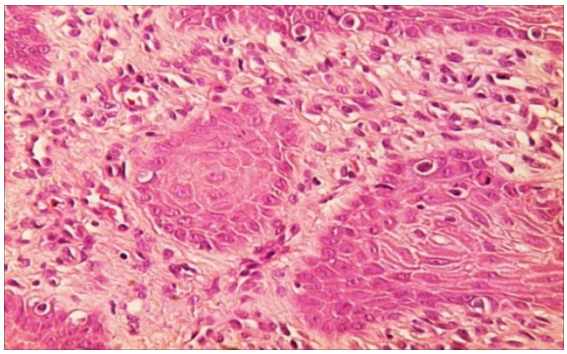

Fig.4. Pseudoepitheliomatous hyperplasia- epithelial pearls as aggregates of keratinized spinous cells. HE staining x200

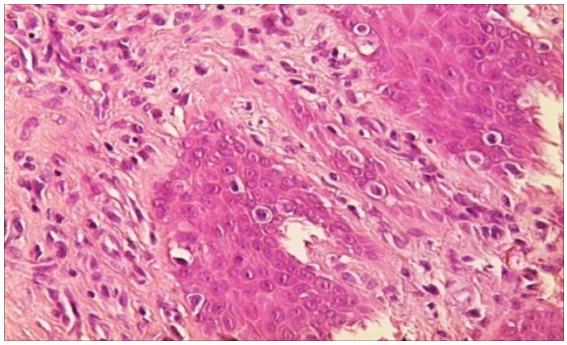

Fig.5. Pseudoepitheliomatous hyperplasia- dyskeratosis. HE staining x40

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Morphological changes of the underlying lamina propria (Fig.6).

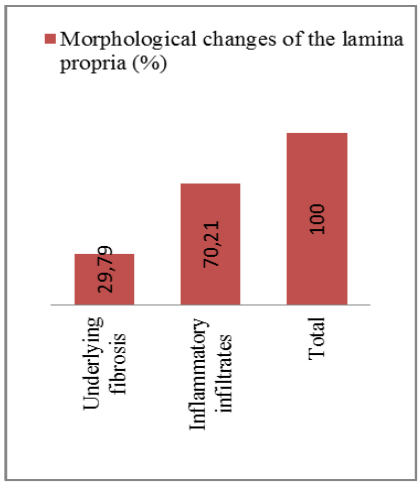

Fig.6. Morphological changes of the lamina propria

In 14 cases (29.78%) we observed the underlying fibrosis of the hyperplastic epithelium, consisting in the presence of collagen fibrous fascicles of variable thickness that cross each other in various angles, among these co-existing variable quantities of inter cellular and fibrocyte matrix (Fig.7) In the cases of inflammatory cause (7 cases) and infectious cause (26) there was associated the presence of a predominantly lymphoplasmocyte inflammatory infiltrate (70.21%) (Fig.8), while in 5 cases of pseudoepitheliomatous hyperplasia (10.64%) there was observed in the lamina propria the existence of a reactive vascular proliferation, consisting of the presence of numerous small caliber, capillary-like vessels, lined up with swollen endothelial cells and with red blood cells in the lumen.

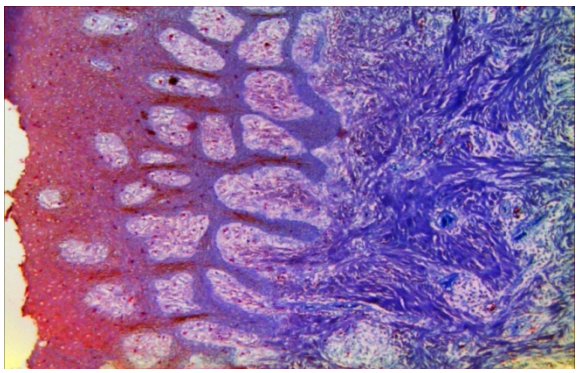

Fig.7. Pseudoepitheliomatous hyperplasia-subepithelial fibrosis. Masson trichrome staining x40

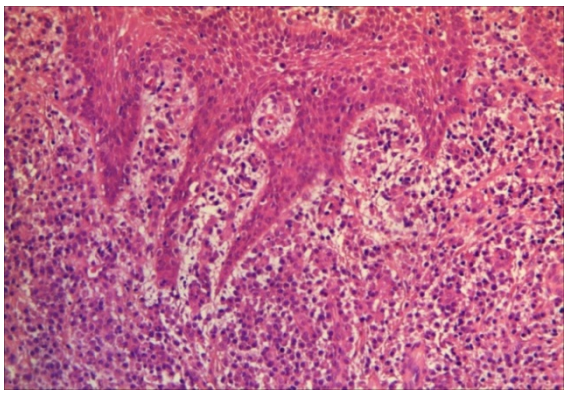

Fig.8. Pseudoepitheliomatous hyperplasia-inflammatory infiltrate. HE staining x100

Histopathological aspects of the lesions associated with oral pseudoepitheliomatous hyperplasia (Fig.9).

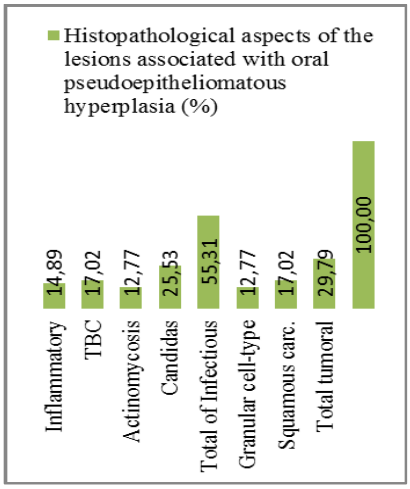

Fig.9. Histopathological aspects of the lesions associated with oral pseudoepitheliomatous hyperplasia

The 47 lesions of pseudoepitheliomatous hyperplasia in the oral mucosa were diagnosed in association with a great diversity of clinical entities, from infectious stomatites (tuberculosis, actinomycosis and candidosis), to chronic inflammatory conditions (oral lichen planus) and to neoplastic lesions, respectively (granular cell tumor and oral squamous carcinoma).

The histopathological aspect of the lesions associated to tuberculosis was the typical one with the presence of specific tuberculous granulomas, with or without necrosis. Tuberculous granulomas were made of giant Langhans cells, epithelioid cells, surrounded by a crown of lymphocytes (Fig.10).

In 6 cases (12.76%), oral lesions of specific pseudoepitheliomatous hyperplasia developed in patients with cervical and facial actinomycosis, the histopathological aspect being the classical one of suppurate actinomycotic granuloma, with

the central presence of a micelle ball surrounded by radially positioned conidia, surrounded by neutrophils and eosinophils resulting in an abscess (Fig.11).

The hyperplastic lesions associated to candidosis were diagnosed in 12 patients with oral candidosis (25.53%) (Fig.12), and in 7 cases (14.89%), oral pseudoepitheliomatous hyperplasia was associated with lichen planus (Fig.13). Oral pseudoepitheliomatous hyperplasia was associated with granular cell tumor (6 cases), and in 8 cases was associated with squamous carcinoma.

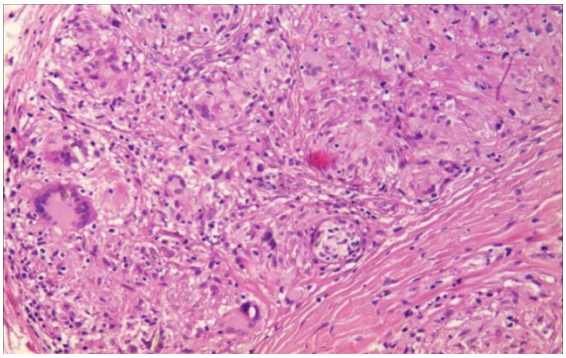

Fig.10. Pseudoepitheliomatous hyperplasia associated with tuberculosis. HE staining x100

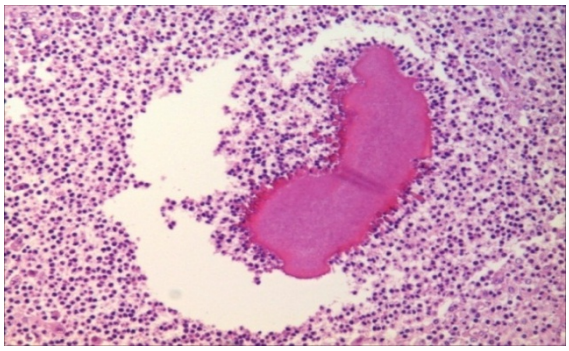

Fig.11. Pseudoepitheliomatous hyperplasia associated actinomycosis-actinomycotic specific granuloma. HE staining x100

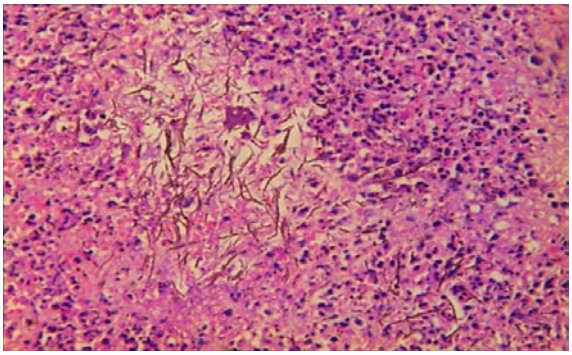

Fig.12. Pseudoepitheliomatous hyperplasia associated with candidosis-chronic inflammatory infiltrate in the lamina propria with lymphocytes, plasmocytes and epitheliod cells with the presence of Candida spores and hyphe. HE staining x 200

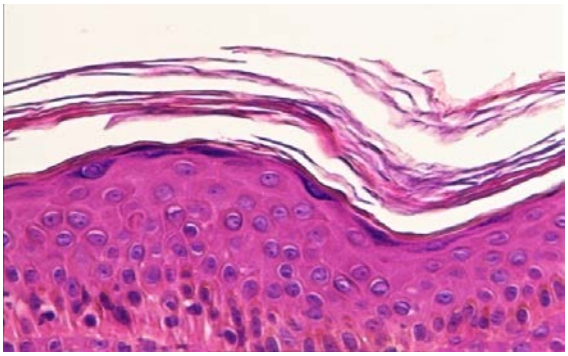

Fig.13. Pseudoepitheliomatous hyperplasia assorted with oral lichen planus-acanthosis, hyperkeratosis. HE x100

Discussion

Discussion regarding the histopathological aspects of oral pseudoepitheliomatous hyperplasia.

In 1986, doctor Unna describes the first case of pseudoepitheliomatous hyperplasia as an “epidermal proliferation covering a lesion of lupus vulgaris” [4].

Various studies indicated the origin of this lesion in the inter follicular epithelium, the ecrine units and other skin appendages [5]. A series of authors consider that skin pseudoepitheliomatous hyperplasia could have its origin both in the epidermis and in the skin appendages [6,7], while others observed the development of such lesions from the mucous surfaces rich in salivary glands, thus suggesting their possible glandular origin [8]. Some studies have also indicated in the conjunctive epithelial support tissue the presence of mast cells, squamous metaplasia of the skin structures epithelium, the involvement of pilous follicles, of sebaceous and sweat glands, of mucous glands and the absence of vascular, lymphatic and perineural invasion [9]. White and Weidman (1926) described a histological grading of these lesions in three types, extremely similar characteristics with the ones of the well differentiated squamous carcinoma [2]. There is also described an atypical variant of pseudoepitheliomatous hyperplasia, where the elongation of the epithelial apexes is made deeply in the underlying conjunctive tissues [10]. Bony pseudoepitheliomatous hyperplasia could be another rare variant appeared as a complication of fistulae chronic ostheomyelitis of the long bones [3,11].

In the investigated cases, the most characteristic aspect of pseudoepitheliomatous hyperplasia with oral localization was observed in the elongation of the epithelial apexes deeply descending into the lamina propria, some of

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these inter crossing with a cribriform aspect. Another change constantly observed was the acanthosis in the intermediary layer and the presence of keratin pearls. In only 15% of the cases, we highlighted the presence of dyskeratosis cells in the intermediary layer, and in 10.64% there were present cytological atypias and rare typical mytoses. Subepithelially, we observed the almost constant presence of an inflammatory infiltrate, mainly a chronical inflammatory infiltrate one, and in almost 30% of the cases, there was associated a discrete fibrosis, while in 10.64% of the investigated cases there was also observed a reactive vascular proliferation.

Discussion regarding the etiopathogenic conditions associated to oral pseudoepitheliomatous hyperplasia.

In 2011, Zayour and Lazova grouped the etiopathogenic conditions associated to pseudoepitheliomatous hyperplasia into 4 large categories: (i) infectious, (ii) neoplastic, (iii) dermatoses with chronic rashes and inflammations and (iiii) various other pathological processes [12].

Infectious diseases that may be associated to skin and mucosa pseudoepitheliomatous hyperplasia are bacterial, fungi, viral and parasitic infections [4]. The most frequent are the ones associated with micro bacteria infections [13].

Most skin deep mycoses (North American Blastomycosis, Paracoccidioidomycosis, Chromoblastomycosis, Phaeohyphomycosis) associate, alongside the intra epidermis absceses, the suppurate dermis inflammation and lesions of pseudoepitheliomatous hyperplasia [14,15,16,17]. In the case of viral infections, the association with pseudoepitheliomatous hyperplasia proved to be a rare one. There were reported such cases in association with the simplex herpes virus (1 and 2) in the immune suppressed patients [18].

The pseudoepitheliomatous hyperplasia lesions were also described in the patients with skin parasite infestations.

The tumor lesions associated with pseudoepitheliomatous hyperplasia include both benign and malignant entities. Frequently observed are the associations between pseudoepitheliomatous hyperplasia and the granular cell tumor [19], but there were also described lesions of pseudoepitheliomatous hyperplasia associated with melanocytarian nevi and especially with Spitz nevi [20,21]. The number of malignant tumors associated with pseudoepitheliomatous hyperplasia is much larger, including the malignant melanoma, lymphoproliferative diseases, basocellular carcinoma, the malignant variant of the clear cell hydradenoma.

Pseudoepitheliomatous hyperplasia may be also found in a series of inflammatory pathogenic conditions, the specialized literature reporting associations of pseudoepitheliomatous hyperplasia with various other lesions like dermatoses and chronic lesions caused by burns.

In our study, oral pseudoepitheliomatous hyperplasia proved to be a rare lesion, its incidence in oral maxillofacial pathology within the Emergency Clinical Hospital of Craiova being under 1% (0.87%). The 47 lesions of pseudoepitheliomatous hyperplasia from oral mucosa were diagnosed in association with a great variety of clinical entities, going from infectious stomatites to chronic inflammatory conditions and to neoplastic lesions, respectively. The most frequent associations were with infectious stomatities, diagnosed in 55.31% of the cases, of which 17.02% were associated with tuberculosis, 12.76% with actinomycosis and 25.53% with Candida. On the second place there were the associations with oral neoplastic conditions, diagnosed in 29.78% of the cases, the most frequent associations being with the oral squamous carcinoma, found in 17.02% of the cases, followed by the association with granular cell tumor, diagnosed in 12.76% of the cases.

As chronic inflammatory conditions associated with oral pseudoepitheliomatous hyperplasia, in our cases there highlighted only the association with oral lichen planus, diagnosed in 14.9%.

Conclusions

The presence of a histopathological frame composed of elongated epithelial apexes, acanthosis, keratosis pearls, dyskeratosis, inflammatory infiltrate, fibroses, requires, in many cases, the differentiation between pseudoepitheliomatous hyperplasia and squamous carcinoma, completely different lesions regarding prognosis and treatment. The etiopathogenic conditions associated with oral pseudoepitheliomatous hyperplasia were: oral candidosis, oral dissemination tuberculosis, oral squamous carcinoma, oral lichenus planus, actinomycosis with oral determinations and granular cell tumor. The presence of such etiopathogenic associations requires the performance of a minute histopathological

diagnosis necessary both for establishing a clear etiology, and also for avoiding a diagnosis error with a negative impact on the health state of these patients.

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