THE IMPORTANCE OF PATHOHISTOLOGY IN EARLY DIAGNOSIS OF ORAL PEMPHIGUS

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Summary. Pemphigus vulgaris (PV) is autoimmune disease, where antibodies are produced against keratin and adhesive molecules of intercellular substance in skin epidermis and epithelium of oral mucous membrane. Disease progression can be slower if there are only oral changes, without other clinical manifestations, which can interfere with diagnosis and involves a lot of differential and diagnostic possibilities, as well as therapy hesitations. The aim of our work was to do pathohistological verifications of oral lesions, in order to set up early and certain PV diagnosis and to give adequate therapy. Material was presented by 14 biopsies taken from the patients with oral changes, which clinically pointed to PV. Hematoxilin-eosin staining was used. They show characteristic pathohistologic changes by forming acantholytic bullae in intercellular areas of spinal epithelium layer. The bottom of bulla presents basal layer, but the roof the other parts of epithelium. In bulla contents, individual or in groups acantholytic cells can be seen. Pathohistological findings set up the certain diagnosis of PV, when there are only changes on oral mucosa membrane, or in discrete combination with other mucosa membrane, without skin lesion, which gives patients direction to dental clinics.

Key words: Pemphigus, oral mucosa membrane, pathohistological verification

Introduction

Pemphigus vulgaris (PV) is the most common disease variation of pemphigus group, chronical course and bad prognosis, with therapeutic and spontaneous remissions, yet with lethal results. Mortality is about 100% without therapy, and without it, it is ranged from 5 to 25%. The percentage is lessened to 6% (1,2,3) with introduction of immunosuppressive therapy.

Disease etiology was sufficiently explained. It is autoimmune bulla disease where antibodies are produced against keratin adhesive molecules of intercellular substance in skin epidermis as well as in oral mucosa membrane epithelium. These autoantigens are desmoglein 3 (Dsg-3) for Pemphigus Vulgaris and desmoglein 1 (Dsg-1) for Pemphigus Follicaeus. They are complex of molecules built in desmosomes. Acatholyse mechanism is started by antibody connection, which usually belongs to class IgE, for specific antigens in intercellular substance, which presents stimulation for keratinocytes. Synthesis is activated as well as proteinasis relief, which is clearer plasminogen activator. Plasminogen transforms into plasmin which separates intercellular proteins, which are responsible for intercellular cohesion. In this way acantholysis and interepithelium rupture are produced. These antibodies can be detected in patients’ serum and their titre is usually followed by disease deterioration (3,4,5).

Some authors emphasize disease association with enclosed HLA typisation. There is always the question about virus role as the potential cause for appearance and development of the disease (2,6,7).

In 50-70% cases, changes begin in oral cavity where bullae, especially retromolar spontaneously appear on unchanged mucous membrane. Bullae quickly spread, leaving wide erodent areas which are very painful and disturb the process of speaking and mastication (8,9). All parts of oral cavity have been caught by erodent surface, which can be noticed on oropharings, and gingiva as well (10). Gradually, the changes appear, starting with oral cavity, eyes, nasal mucosa membrane, and even on genitals and rectum (2,3,6,10,11). Over a period of several weeks, months, years oral changes can progress and affect healthy skin. Critical surfaces can be toryo, capillitium and axils. Bullae rupture leave painful erosions, which can be secondary infected.

It is very difficult to establish accurate diagnosis of oral manifestation. Numerous forms of dermatitis in the mouth can be manifested by similar clinical picture. Differential diagnosis of changes which are found in oral mucosa membrane includes: Cicatrical Pemphigoid, Pemphigoid bullous, Dermatitis herpetiformis During, Erythema exudativum multiforme, Lichen planus, Gingivostomatitis herpetica and so on.
Material and Methods

Fourteen patients have been treated, six females and eight males. They were between 30 and 70 years of age. All patients were treated at the Department of Parodontology and Oral Medicine, Dental Clinic, Niš.

The patients had had oral changes for several months and they were treated with local therapy or with antibiotics but without any betterment. After the complete examination including anamnesis, laboratory results, the way of changes appearance, clinical mucosa membrane appearance, mechanical sufferings after dental treatment (suspicion on Nikolski’ phenomenon), PV was suspected.

In order to establish the right diagnosis, biopsy was taken from all the patients, which always included a part of lesion and a part of unchanged mucosa membrane as well. Biopsy was mainly taken from buccal mucosa membrane. Further material treatment was done according to standard principles for pathohistological analysis. Dying was conducted microscopically at the Institute of Pathology, Medical Faculty, Niš.

Results

Diagnosis was established according to anamnesis, clinical examination and pathohistological results. According to anamnesis data, changes lasted from fifteen days to six months. They were manifested like blisters and lesions which appeared suddenly, or after some light flu, with stinging in the throat. Changes in all patients are presented in the table 1.

At the moment of examination, there were diffuse erodent surfaces, covered with serofibrinous exudations, the top of bullae, spittle and bits of food, on cheeks and retromolar (Fig. 1).

There are also residual erodents with fretted edges which were localized on soft palate, palatal arches and uvula, with tendency to spread into oropharynx. As a consequence of painful, sensitive mouth, inadequate oral hygiene, and lack of mashy and liquid food, the tongue is coated with filthy-greyish layers (Fig. 2).

<table>
<thead>
<tr>
<th>No</th>
<th>Sex</th>
<th>Age</th>
<th>Period from appearance to diagnostification</th>
<th>Oral mucous membrane</th>
<th>Eye, nose, genital</th>
<th>Skin</th>
</tr>
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<tr>
<td>1</td>
<td>m</td>
<td>1951</td>
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<td>erodent surfaces</td>
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<td>no</td>
</tr>
<tr>
<td>2</td>
<td>f</td>
<td>1973</td>
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<td>no</td>
</tr>
<tr>
<td>3</td>
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<td>1935</td>
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<td>wide erosions</td>
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<td>no</td>
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<td>4</td>
<td>f</td>
<td>1928</td>
<td>fifteenth days</td>
<td>erosions, paraneoplastic shape, exitus in 3 months</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>5</td>
<td>m</td>
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<td>erodent surfaces</td>
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<td>6</td>
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<td>eye</td>
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<tr>
<td>7</td>
<td>m</td>
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<td>eye</td>
<td>yes</td>
</tr>
<tr>
<td>8</td>
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<td>1957</td>
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<td>erosions</td>
<td>eye</td>
<td>no</td>
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<tr>
<td>9</td>
<td>m</td>
<td>1929</td>
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<td>cheek mucous membranae, throat</td>
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<td>no</td>
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<tr>
<td>10</td>
<td>m</td>
<td>1940</td>
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<td>mucous membranae of hard palate</td>
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<tr>
<td>11</td>
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<td>1948</td>
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<td>eye, nose</td>
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<td>13</td>
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<tr>
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<td>m</td>
<td>1956</td>
<td>a month</td>
<td>oral mucous memhrabae</td>
<td>eye</td>
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</tr>
</tbody>
</table>

Fig. 1. Erodent surfaces with bits of top of bullae in retromolar trigonium

Fig. 2. Coated tongue with bulla reminders and erosions; on mouth semimucous present crust

These signs of periodontal disease are clearly manifested because of plaque deposit and teeth treatment delay until the changes are healed. Pathohistological examinations of biopsy material were done in 13 patients (one of the patients had already had diagnosis of skin lesions). The results of pathohistological examinations showed characteristic changes of PV.

Histologically, the blister in pemphigus vulgaris is formed due to separation of the stratum spinosum and
outer epidermal layers from the basal layer (suprabasal dyshesion). The basal cells remain adherent to the basal lamina resembling tombstones. The blister contains a moderate number of lymphocytes, macrophages, eosinophils, and neutrophils. Distinctive, round epithelial cells, called acantholytic cells, are shed into the vesicle during the process of dyshesion. In addition to spongiosis (increased fluid between keratinocytes, accentuating the intercellular spinous connections), eosinophils may be present in the epithelium (eosinophilic spongiosis). The subjacent lamina propria shows a moderate infiltrate of lymphocytes, macrophages, and neutrophils, predominantly around blood vessels (Fig. 3).

Discussion

Numerous authors gave various data about primary oral disease manifestation, which can last for days, and months. Changes appearance can be seen only in oral cavity in patients up to 70% (3,8,12,13). The authors treated a patient, who developed skin changes only after four years. Glickman cites that lesions of mucosa membrane preceded skin lesions (14). Laskaris and Shklar cite that PV appears in more than 68% on oral mucosa membrane, proceeding several weeks, months or even a year before skin manifestations appear. It was also confirmed that Mediterranean population is mostly affected (female more than male, the average age is 54,4) (13). Kansky and assistants also emphasize that erosions on oral cavity mucosa membrane preceede skin lesions (6).

A very important question for discussion is that the right diagnosis for the same disease requires different time, depending on whether disease appears in oral cavity or on skin.

If disease is located on skin, diagnosis can be established much faster. But in case of oral changes, much more time and team of consultants are required in order to set up the final diagnosis. Ettlin D, cites that in 30 patients with oral changes, as an early sign of disease, interval for final diagnosis was less than six months for 17 patients (57%), six to twelve months in four patients (13%) and more than a year for nine patients (30%). In our cases, proportion is somehow better, because all 13 patients an adequate diagnosis was obtained in interval of six months (9).

It is considered that the fastest diagnosis is pathohistology, because of differentially diagnostic similarity to numerous diseases in oral cavity. Clinical and pathohistological results of this study are in accordance with the results of numerous authors who describe oral changes like: loss of intercellular adherence of suprabasal spinous cells (acantholysis), formation of clefts immediately superficial to basal cells and extension of clefts to form intraepithelial vesicles (1,2,3,15,11,16,17). The most important differentially diagnostic characteristic is that in PV there is interepithelial rupture, while in other diseases which can be taken into consideration, the rupture is subepithelial.

To confirm the diagnosis, direct immunofluorescence of lesion and perilesion changes are done, which most often show deposit IgG in intercellular areas of spinous epithelial layer.

Conclusion

1. Pemphigus vulgaris is relatively frequent dermatitis with initial changes on oral mucosa membrane.
2. Due to similarity to other diseases, clinical sight with wide erodent areas in the mouth, makes it difficult for the general dentist to confirm the diagnosis.
3. In order to set a quick diagnosis, good anamnesis and clinical examination are required. Pathohistological analysis of biopsy material of oral cavity, should include not only changed mucosa membranes but material taken from healthy tissue as well.
4. Direct immunofluorescence should be done wherever there are possible conditions.
ZNAČAJ PATOHISTOLOGIJE U RANOJ DIJAGNOSTICI ORALNOG PEMFIGUSA

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Kratak sadržaj: Pemphigus vulgaris (PV) je autoimuno oboljenje, kod koga se stvaraju autoantitela protiv keratinocitnih adhezivnih molekula intercelularne supstance u epidermu kože i epitelu oralne sluzokože. Progresija bolesti može biti sporija ako postoje samo oralne promene, bez drugih kliničkih manifestacija, što otežava dijagnozu i uključuje niz dijagnostičkih mogućnosti, kao i terapijske nedoumice. Cilj našeg rada bio je da se uradi patohistološka verifikacija oralnih lezija, radi postavljanja rane i sigurne dijagnoze PV i uključi adekvatna terapija.

Ključne reči: pemphigus, oralna sluzokoža, patohistološka verifikacija

References