FACTA UNIVERSITATIS
Series: **Medicine and Biology** Vol.13, No 3, 2006, pp. 177 - 180 UC 616.527

THE IMPORTANCE OF PATHOHISTOLOGY IN EARLY DIAGNOSIS OF ORAL PEMPHIGUS

Draginja Kojović[1], Ana Pejčić[1], Dragan Mihailović[2], Dragan Mikić[3]

[1]Department of Parodontology and Oral Medicine, Medical Faculty, University of Niš
[2]Institute of Pathology, Medical Faculty, University of Niš
[3]Clinic of Dermatovenerology, Military Hospital, Niš
E-mail: dpejca@nadlanu.com

Summary. *Pemphigus vulgaris (PV) is autoimmune disease, where antibodies are produced against kreatin 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 showed 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 membranae, 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 Foliaceus. 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 rapture 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 bullosus, 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 Paradontology 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).

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

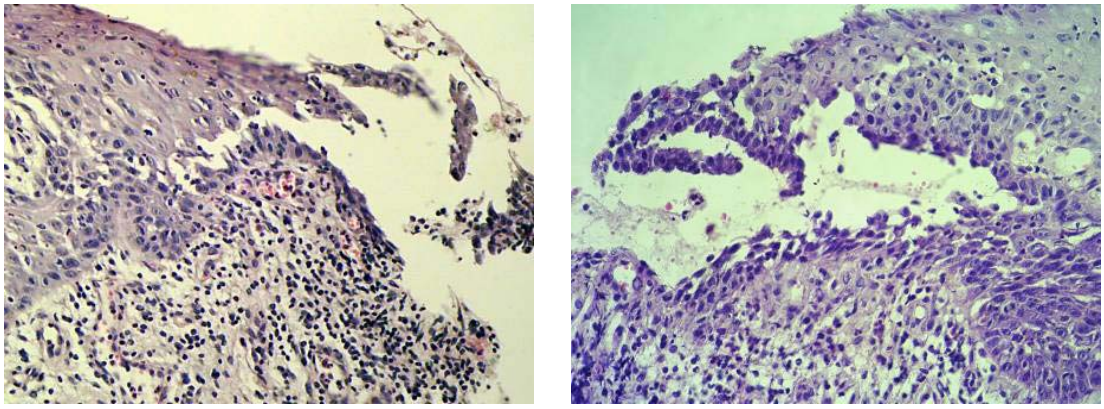
Fig. 2. Coated tongue with bulla reminders and erosions; on mouth semimucous present crust

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

Table 1. Localization and duration of changes on skin and mucous membrane

N°	Sex	Age	Period from appearance to diagnostification	Oral mucous membranae	Eye, nose, genital	Skin
1	m	1951	two months	erodent surfaces	no	no
2	f	1973	fifthteen days	erosions, oral cavity base	no	no
3	f	1935	four months	wide erosions	no	no
4	f	1928	fiftheen days	erosions, paraneoplastic shape, exitus in 3 months	yes	yes
5	m	1930	three months	erodent surfaces	no	no
6	m	1953	a month	erosions	eye	no
7	m	1951	four months	retromolar erosions	eye	yes
8	m	1957	three months	erosions	eye	no
9	m	1929	three months	cheek mucous membranae, throat	no	no
10	m	1940	five months	mucous membranae of hard palate	no	yes
11	f	1948	six months	palate, tongue	eye, nose	no
12	f	1958	two months	retromolar gingiva	genital, rectum	no
13	f	1928	two months	erosions	no	yes
14	m	1956	a month	oral mucous memebrabae	eye	yes



a) b)

Fig. 3. Pemphigus vulgaris. Suprabasal dyshesion reveals crispy delineated basal epithelial cells slightly separated from each other and totally separated from stratum spinosum. Hematoxilin-eosin, (a) ×180; (b) ×560

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 precede 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 adherance of suprabasal spinous cells (acantholysis), formation of clefts immidiately superficial to basal cells and extension of clefts to form intraepithelial vesicles (1,2,3,15,11,16, 17). The most important differentally 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 ralatively frequent dermatitis with initial changes on oral mucosa membranae.

2. Due to similaity 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 examinationare required. Pathohistological analysis of biopsy material of oral cavity, should include not only changed mucosa membranae but material taken from healthy tissue as well.

4. Direct immunofluorescence should be done wherever there are possible conditions.

References

1. Cawson RA, Odell EW. Diseases of the oral mucosa: non-infective stomatitis. In: Cawson RA, Odell EW (eds), Oral pathology and oral medicine. Churchill Livingstone, Edinburgh, London, New York, Philadelphia, St. Louis, Sydney, Toronto, 2002: 192-215.
2. Orlov S, Kojovic D, Mirkovic B. The group of pemphigus diseases. In: Orlov S, Kojovic D, Mirkovic B (eds), Oral medicine. Nis, 2001: 129-145.
3. Binic I. Bullous dermatosis. In: Paravina M, Spalevic Lj, Stanojevic M, Tiodorovic J, Binic I, Jovanovic D (eds), Dermatovenerology. Prosveta, Nis, 2003: 199-210.
4. Harman KE, Gratian MJ, Bhogal B, et al. A study of desmoglein 1 autoantibodies in Pemphigus vulgaris and the association with a more severe phenotype. Br J Dermatology 2000; 143: 348-350.
5. Harman Ke, Gratian MJ, et al. The transitions of Pemphigus vulgaris into Pemphigus foliaceus: a reflection of changing desmoglein 1 and 3 autoantibodies levels in Pemphigus vulgaris. Br J Dermatology 2002; 147(4): 836-839.
6. Kansky A. Bullous dermatosis. In: Kansky A, et al (eds), Skin and veneral diseases. JUMENA, Zagreb,1984: 165-170.
7. Miyagawa S, Niireki H et al. Genotyping for HLA-A, B and C alleles in Japanese patients with pemphigus: prevalence of again alleles of HLA-B15 family. Br J Dermatology 2002; 146: 52-58.
8. Dostanic I, Dostanic N. Autoimmunous diseases - Autoagressive diseases. In: Dostanić I, Dostanić N (eds), Dermatovenerology. Beograd 1998: 95-108.
9. Ettlin D. Diagnostic patterns in Pemphigus vulgaris. Northwestern University Dental School, Chicago, Illinois, 1999.
10. Castellanos JL et al. Gingival disorders of immune origin. Medicina Oral 2002; 7: 271-283.
11. Regezi JA, Sciubba JJ. Malattie vesicicolo-bollose. In: Regezi JA, Sciubba JJ (eds), Patologia orale. WB. Saunders Company, Philadelphia, Pennsylvania, 1999: 1- 23.
12. Salomon T. Skin diseases and mouth. In: Topic B, Arifhodzic F, Cekic-Arambasin A, Cokorilo N, Dautovic S, Dedic A, Malic M, Piranic H, Salomon T (eds), Oral medicine. Dentistry Faculty Sarajevo 2001: 289-315.
13. Laskaris G. Color Atlas of Oral Diseases. Thieme Medical Publishers, Inc, Stuttgart, New York, 1994: 198-226.
14. Glickman S, Carranza JR with contributions by 14 authorities. The oral manifestations of dermatologic disease. In: Glickman S, Carranza JR (eds), Clinical periodontology. WB Saunders Company, Philadelphia, London, Toronto, 1979: 155-193.
15. Lombardi ML, Mercuro O, Ruocco V, et al. Common human leukocyte antigen alleles in Pemphigus vulgaris and Pemphigus Foliaceus in Italian patients. J Invest Dermatol 1999; 113: 107-110.
16. Hernandez G, Arriba de la Fuente L, Lucas M. Bullous diseases of the oral mucosa. Clinical, histological and immunological differential characteristics. Medicina Oral 1999; 4: 528-551.
17. Martel P, Cordel N, et al. Pemphigus with clinical, histological and immunological features of 60th vulgaris and foliaceus subtypes. Br J Dermatology 2002; 147: 1263-1269.

ZNAČAJ PATOHISTOLOGIJE U RANOJ DIJAGNOSTICI ORALNOG PEMFIGUSA

Draginja Kojović[1], Ana Pejčić[1], Dragan Mihailović[2], Dragan Mikić[3]

[1]Odeljenje za Parodontologiju i oralnu medicinu, Medicinski fakultet, Univerzitet u Nišu
[2]Institut za Patologiju, Medicinski fakultet, Univerzitet u Nišu
[3]Klinika za Dermatovenerologiju, Vojna bolnica, Niš
E-mail: pejca@eunet.yu

Kratak sadržaj: *Pemphigus vulgaris (PV) je autoimuno oboljenje, kod koga se stvaraju autoantitela protivu 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 diferencijalno 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 Materijal je činilo 14 biopsija uzetih od pacijenata sa oralnim promenama, koje su klinički ukazivale na PV. Korišćena je Hematoxilin-eosin metoda bojenja. Pokazali su karakteristične patohistološke promene sa formiranjem akantolitične bule u intercelularnim prostorima spinoznog sloja epitela. Dno bule predstavlja bazalni sloj a krov ostali delovi epitela. U sadržaju bule vide se pojedinačne ili u grupama epitelne akantolitične ćelije. Patohistološki nalaz postavlja sigurnu dijagnozu PV-a, kada su promene samo na oralnoj sluzokoži, ili u diskretnoj kombinaciji sa drugim sluzokožama, bez kožnih lezija što pacijenta obično upućuje u stomatološke ambulante.*

Ključne reči: *pemphigus, oralna sluzokoža, patohistološka verifikacija*