Clinical analysis of patients with pemphigoid-like ophthalmological symptoms

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Abstract

PURPOSE: The aim of this study was a clinical analysis of patients with symptoms typical of pemphigoid.
MATERIAL AND METHODS: 21 patients were enrolled on the study within the period 1988-2004. The frequency and type of ophthalmological and extraocular symptoms and accompanying diseases were assessed. The analysis also contains immunological findings as well as administered treatment.
RESULTS: Ophthalmological changes were detected in 100% of examined patients with pemphigoid. The most frequent were dry eye syndrome and conjunctivitis. Immunohistochemical tests revealed the presence of antibodies in 68,2% of the examined cases. All patients required specific treatment – local, general and surgical. Despite the administered therapy the development of cicatricial changes was observed.
CONCLUSIONS: Chronic conjunctivitis and keratitis require diagnostics into pemphigoid. Intensive therapy is necessary in patients with ocular cicatricial pemphigoid (OCP) because of high risk of blindness. Delayed diagnostics disable immunohistochemical confirmation of disease.

Introduction

Cicatricial pemphigoid is a chronic, progressive and rare disease. The most typical symptoms are pathologies of skin and mucous membrane which regress with cicatrization. The frequency of this pathology is estimated as 1:20000 [10]. It usually affects people of 40 years old and more, mostly women. The pathogenic mechanisms of ocular cicatricial pemphigoid are incompletely understood. Antibasement membrane antibodies which lead to subepithelial blistering, granulation tissue and inflammatory infiltrate formation in the substantia propria are thought to be the main pathophysiological mechanisms in ciciatricial pemphigoid . It has been found eosinophils and increased collagen type I and III. Human leukocyte antigen HLA-DR2, HLA-DR4 and DQw7 genotypes have been identified as conferring increased susceptibility to the development of this disease. Ocular cicatricial pemphigoid (OCP) is one of the forms of bullous pemphigoid. Initial symptoms of ocular pemfigoid are not characteristic, affecting conjunctiva in the first stage as a chronic conjunctivitis which is not responsive to treatment. Conjunctival fibrosis leads to cicatrisation of conjunctival sac, dry eye syndrom, trichiasis, entropion, ectropion, corneal epithelial erosions or ulceration and keratinization of cornea,

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leading to permanent deterioration of aquity of vision, which may result in blindness [10, 14].

Secondary glaucoma is one of the most frequent complications. Ocular cicatricial pemphigoid may be chronic, acute, or subacute disease with periodic exacerbation of conjunctival inflammation.

Detection of antibodies of class IgG, less frequently IgA and C3-complement in a basement layer of conjunctiva is the most important diagnostic test which confirms diagnosis when combined with typical ophthalmological symptoms of this pathology [3, 5, 6, 7, 13, 16, 17].

Treatment of cicatricial pemphigoid is long-lasting and not very effective. Only in few cases patients retained sufficient aquity of vision[12, 13, 14]. The important thing is that a disease affecting eyes requires both local and general treatment at the early stage, because potential changes are irreversible. The treatment in this disease are topical drops or ointment (lubricants, corticosteroids, antibiotics, antiglaucomatous). Oral Dapsone and corticosteroids may control the activity of the disease. In other progressive cases immunosuppressive drugs must be used (azathioprine, cyclophosphamide, methotrexate, mycophenolan mofetil, daclizumab, intravenous immunoglobulin therapy).

The aim of the study is a clinical analysis of patients with chronic conjunctivitis and keratitis which both lead to cicatrisation. The ophthalmological changes where assessed as well as the administered treatment - local, general and surgical.

Material and methods

21 patients (12 women, 9 men, 42 eyes) diagnosed and treated in Department of Ophthalmology, Medical University of Warsaw were analyzed within the period 1988- 2004. The age of patients ranged from 23 to 97, the mean value 59 ±17,87. Duration of the disease ranged from 0,25 to 16 years, the mean value 7,3 ± 4,97.

The frequency and type of ophthalmological changes in the anterior part and fundus of the eyes, extraocular symptoms (skin and mucous membranes lesions) and accompanying diseases were examined.

Diagnostic tests (immunohistochemical tests), pharmacological (local and general) and surgical therapy administered to individual patients were evaluated.

McNemara test was used in statistic analysis to compare the frequency of assessed features in two paired matches. Statistical significance was determined using Chi^2 test with p=0.05 as a border value.

Results

Presence of ophthalmological lesions was detected in all 21 patients (100%) suffering from symptoms typical of cicatricial pemphigoid. Dry eye syndrome and conjunctivitis were the most frequent symptoms. The frequency of individual ophthalmological changes is presented in Table I.

Ocular symptoms were preceded by pathologies on mucous membrane in the case of 7 patients (33,3%) and skin pathologies in the case of 5 (23,8%). In few cases accompanying diseases were diagnosed, such as asthma, chronic catarrh, diabetes, psoriasis and laryngeal fibrosis. In 15 caseas (68,2%) biopsy of conjunctiva proved presence of IgG antibodies. IgA antibodies were detected in 3 of these patients (13,6%), IgM antibodies in 2 (9%) and C3 complement in 5 patients. These findings confirmed the diagnosis of pemfigoid. All patients affected by ophthalmological symptoms (n=21, 100%), required administration of local treatment. Artificial tears (52,4%), antibiotics (38%), hypotensors of intraocular pressure (33,3%), corticosteroids (28,6%) and nonsteroid anti-inflammatory drugs (19%) were most frequently

Table I. The frequency of ophthalmologial symptoms in patients with pemphigoid.

	1st examination		During treatment	
Ophthalmological symptoms	**N**	**fraction**	**N**	**fraction**
coniunctivitis	13	0.61	6	0.28
symblepharon	8	0.41	18	0.85
decreased lacrimation	21	1.00	21	1.00
epitheliopathy	4	0.19	3	0.14
keratitis	4	0.19	4	0.19
corneal ulceration	3	0.14	3	0.14
neovascularization	3	0.14	3	0.14
eye-bulb ulceration and perforation	1	0.05	-	-
ektropion and trichiasis	2	0.09	4	0.19
entropion	1	0.05	0	0.00
ptosis	1	0.05	1	0.05
increased infraorbital pressure	2	0.09	2	0.09
ankyloblepharon	1	0.05	1	0.05

N – number of patients

administered. Few patients underwent subconjunctival injections of bromhexine. Lunar caustic, solcoseryl and cyclosporine were administered.

15 patients (71,4%) required implementation of general treatment. Steroids (93%, mostly prednisone), sulfons (66,7%, dapson) and other immunosuppressive drugs (26,7%, mostly cyclofosfamid) were the most frequently implemented. In few cases vitamins (PP, E), nonsteroid anti-inflammatory (phenylbutazone) and antiviral drugs (acyclovir) were used.

8 patients (38%) underwent surgical treatment. Frequency and type of surgical therapy are presented in Table II.

The observation confirmed the improvement of the condition in 5 patients (24%), deterioration of 6 (28%) and in 10 (48%) no major changes were observed (Figure 1).

Examination of individual patients proved that symblepharon was the only symptom whose frequency changed significantly as a result of the administered treatment.

Changes in frequency of other symptoms are presented in Table III. Rare symptoms such as entropion and ectropion of the eyelids, ancyloblepharon and perforation of the eyeball as a result of corneal ulceration are not listed in the Table III.

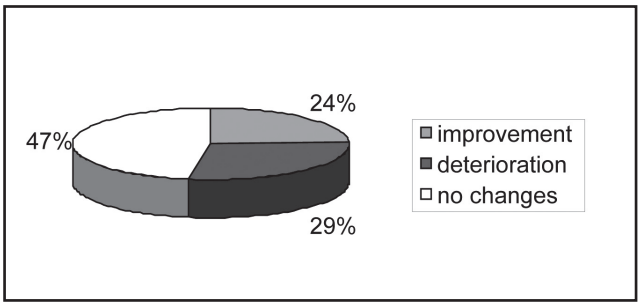

Figure 1. Results of clinical patients observation during therapy.

Discussion

As the above analysis proves pemphigoid-like ocular symptoms were diagnosed in all patients (100%) examined in Department of Ophthalmology. According to Thorn and co-authors, symptoms typical of ocular cicatricial pemphigoid coexist with the lesions on the mucous membranes in 82,4% [18]. Similarly to Miserocchi and Thorn's findings on frequent coexistence of extraocular pathologies (50-82,4%), in the analyzed group of patients these changes were observed in 12 cases (57,1%), and in 9 of these 12 patients pemphigoid was confirmed (42,8%) by immunohistochemical analysis. Miserocchi's study demonstrated that 50% of patients affected by OCP, suffered from extraocular diseases [9].

Cicatrization in the anterior part of the eye may occur in the course of the many other diseases and may pose a serious problem in diagnostics and treatment. Pemphigus foliaceus, lichen planus and Stevens-Johnson's syndrome were diagnosed only in few cases. Biopsy of conjunctiva, immunohistochemical tests, as well as detection of IgG and IgA antibodies (less frequently) and C3-complement in a basement layer are necessary diagnostic, which enables to make a proper diagnosis. It is crucially important to carry out a biopsy of conjunctiva before symblepharon develops, as immunohistochemical examination can be made only on undamaged conjunctiva [1, 3, 5, 15, 17]. Immunohistochemical test confirmed the diagnosis of OCP in 15 cases out of 21 patients affected by pathologies typical of pemphigoid in the anterior part of the eye. The examination of bioptat was impossible in the remaining 6 cases due to advanced cicatrization of conjunctival sac.

Cicatrization of conjunctivae is a significant problem in the course of OCP, because it may lead to numerous complications, such as symblepharon, decreased secretion of lacrimal film, incorrect positioning of eyelids, trichiasis. Administered treatment aims at suppression of pathological process in order to reduce complications. The first examination proved the presence of cicatrisation of conjunctivae in almost 41% enrolled on the study. Despite the administered therapy the percentage of people affected by the above pathologies increased by 85%. Other authors provide similar findings [9, 11]. Elder and co-authors demonstrated that a big dose of prednisolon

Table II. Type of surgical procedures performed in patients with pemphigoid.

Type of procedure	N
obliteration of lacrimal points	1
plastic of coniunctival sac	2
operation of entropion	1
operation of ektropion	1
covering by amniotic membrane	3
corneal transplantation	3
mucosal transplantation	2
covering by silicon band	1

N – number of patients, who underwent surgical procedures

Table III. The assessment of analyzed ophthalmologic symptoms in particular patients during therapy.

Symptoms	Improvement	Deterioration	No changes	p
Conjunctivitis	6	1	5	n.s.
Epitheliopathy	2	1	3	n.s.
Corneal ulceration	3	3	0	n.s.
	1	1	6	n.s.
Symblepharon	5	3	9	<0.05
Trichiasis	2	1	1	n.s.
Corneal erosion	2	2	2	n.s.

and cyclofosfamid are effective in severe conjunctivitis and keratitis, *yet* do not prevent cicatrisation [4].

The majority of patients required administration of artificial tears, considerable percentage of patients required local treatment, such as antibiotics, hypotensors of eyepressure, corticosteroids and nonsteroid anti-inflammatory drugs. 71% of patients required implementation of general pharmacological therapy. Corticosteroids (prednisone) and dapson were most frequently administered drugs, other immunosuppressive drugs were used less frequently and they were used mostly in a final stage of the disease when the ancyloblepharon and keratinization of cornea were identified. Other available findings on general treatment are similar to what the study proved [2, 8, 9, 18]. The therapy with the used of these drugs improves ophthalmological condition of patients. However it may be very encumbering and may result in severe complications [9]. Despite of pharmacological treatment (local and general) many patients require surgical procedures. Entropion, ectropion and trichiasis can be corrected by plastic surgery of eyelids. However it is necessary to remember that surgical procedures carried out on an eyeball, orbit and adnexa, such as cataract or plastic surgery may result in intensification of cicatrization process.

As the above analysis proves, the therapeutical process did not improve the condition of more then 76% of patients affected by pemphigoid-like ophthalmological symptoms. It demonstrates it is a progressive disease and does not often respond to the treatment. It also requires discipline from patients and the doctor and the patient's involvement in the therapeutical process. In the examined group one patient stopped taking the drugs without consulting the doctor. One of the patient did not attend check-up tests for three years and some other patients, contrary to the doctor's orders, did not attend examination regularly. It resulted in intensification of pathological symptoms. The condition of three out of five patients, whose disease was diagnosed at the early stage, improved. Making the diagnosis at the early stage of the disease seems to be an important prognostic factor, because it results in immediate administration of immunosuppressive therapy. Together with proper care it prevents potential complications.

Moreover, patients affected by OCP require frequent ophthalmological examination, not only due to potential progression of pathologies but also to enable the monitoring of the therapy. It is also important because of the higher risk of bacterial infection [9].

Conclusions

1. Chronic conjunctivitis and keratitis non responding to local therapy require immediate diagnostics into cicatricial pemphigoid.
2. Patients affected by OCP require intensive pharmacological or surgical treatment, because its natural course leads to blindness.
3. Advanced ophthalmological lesions detected during the first examination prove that such patients start the diagnostic process usually too late when the immunological confirmation of the disease may be impossible.

REFERENCES

1 Beverly A, Rice C, Foster S. Immunopathology of cicatrical pemphigoid affecting the conjunctiva. Ophtalmology. 1990; **97**:1476-83.
2 Celis Sanchez J, Lopez Ferrando N, Garcia Largacha M, Gonzales del Valle F, Ortiz de la Torre MJ. Subconjunctival mitomycin C for the treatment of ocular cicatricial pemphigoid. Arch. Soc Esp Oftalmol. 2002; **77**:501-6.
3 Cozzani E, Drosera M, Carrozzo M, Gandolfo S, Rebora A. Frequency of IgA antibodies in pemphigus, bullous pemphigoid and mucous membrane pemphigoid. Acta Derm Veneral. 2004; **84**:381-4.
4 Elder MJ, Litman S, Dart JKG. Role of cyclofosfamid and high dose steroid in ocular cicatricial pemphigoid. Br J Ophtalmol. 1995; **79**: 264-6.
5 Hacker-Foegen MK, Zilikens D, Giudice GJ, Lin MS. T cell receptor gene usage of BP180 T lymphocytes from patients with bulous pemphigoid and pemphigoid gestationis. Clin Immunol. 2004; **113**: 179-86.
6 Hisamatsu Y, Nishiyama T, Amano S, Matsui C, Ghohestani R, Hashimoto T. Usefulness of immunoblotting Rusing puriefied laminie 5 in the diagnosis of anti-laminin 5 cicatricial pemphigoid. J Dermatol Sci. 2003; **33**: 113-9.
7 Jablonska S, Chorzelski T. Choroby skory [(Skin Diseases) (in Polish)]. PZWL, Warszawa 1997; 257-8.
8 Letko E, Miserocchi E, Daoud YJ, Christen W, Foster CS, Ahmed AR. A nonrandomized comparison of the clinical outcome of ocular involvement in patients with mucous membrane (cicatricial) pemphigoid between conventional immunosuppressive and intravenous immunoglobulin therapies. Clin Immunol. 2004; **111**: 303-10.
9 Miserocchi E, Baltatzis S, Roque MR, Ahmed AR, Foster CS: The effect of treatment and its related side efects in patients with severe ocular cicatricial pemphigoid. Ophtalmology. 2002; **109**: 111-8.
10 Mondino BJ, Brown SI. Ocular cicatricial pemphigoid. Ophtalmology. 1981; **88**: 95-100.
11 Mondino BJ. Cicatricial pemphigoid and erythema multiforme. Ophtalmology. 1990; **97**: 939-52.
12 Nguyen QD, Foster CS. Cicatricial pemphigoid: diagnosis and treatment. Int Ophthalmol Clin. 1996; **36**: 41-60.
13 Portacha L, Kecik T. Nietypowe postacie pemfigoidu ocznego. [(Atypical forms of ocular pemphigoid) (In Polish with English abstract)] Okulistyka, 2000; **3**: 67-69.
14 Portacha L, Zydecki M, Ciszewska J, Zamlynska A, Lewandowski P, Domoslawski M. Pemfigoid jako przyczyna znacznego uposledzenia ostrosci wzroku. [(Pemphigoid as a cause of marked impairment of visual acuity) (In Polish with English abstract)] Klinika Oczna. 1991; **93**: 266-7.
15 Power WJ, Neves RA, Rodriguez A. Increasing the diagnostic yield of conjunctival biopsy in patients with suspected ocular cicatricial pemphigoid. Ophthalmology. 1995; **102**: 1158-63.
16 Razzaque MS, Foster CS, Razzaque AA. Role of Collagen-Binding Heat Shock Protein 47 and Transforming Growth Factor-ß1 in Conjunctival Scarring in Ocular Cicatricial Pemphigoid. Invest Ophthalm Visual Science. 2003; **44**: 1616-21.
17 Sakuma-Oyama Y, Powell AM, Oyama N, Albert S, Bhogel BS, Black MM. Evaluation of BP 180-NC16a enzyme-linked immunosorbent in the initial diagnosis of bullous pemphigoid. Br J Dermatol. 2004; **151**: 126-31.
18 Thorne JE, Anhalt GJ, Jabs DA. Mucous membrane pemphigoid and pseudopemphigoid. Ophtalmology. 2004; **111**: 45-52.