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Difficulties in the differential diagnosis of granulomatosis with polyangiitis and scarring pemphigoid

Abstract

The article presents a clinical case of a rare pathology. The patient for several years visited various specialists. In connection with a similar clinical picture, multi-organ damage, differential diagnosis was performed between systemic vasculitis (granulomatosis with polyangiitis) and scarring pemphigoid.The mucous membrane of the mouth and nose is involved in the pathological process with granulomatosis with polyangiitis in the form of ulcerative defects, which subsequently lead to deformation of the nose. The danger with this systemic vasculitis is renal damage with the development of nephritis, renal failure. With scarring pemphigoid, eye damage is typical. In granulomatosis with polyangiitis, damage to the organ of vision is also sometimes possible, but mainly in the form of an orbit pseudotumor. Despite the fact that treatment for both forms of pathology involves the use of glucocorticoids and cytostatics, with a scarring pemphigoid, the main care is provided by dermatologists and ophthalmologists, while the diagnosis and treatment of systemic vasculitis is the task of rheumatologists. One of the criteria for a scarring pemphigoid is loss of vision. However, in this case, it was possible to establish a diagnosis, obtain the first positive results of therapy before the patient shows signs of disability. So, there is a hope for the possibility of preserving vision and a favorable outcome. The rarity of the disease and its poor knowledge, difficulties in diagnosis and the absence of certain standards of therapy, this diagnosis requires more attention from the specialists.

Key words: *pemphigoid, granulomatosis with polyangiitis, systemic vasculitis*

Conflict of interests

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Cicatricial pemphigoid is a disease that most often affects women aged over 60 (2.6 per 100 thousand of population). Its incidence in individuals aged over 80 years increases to 15–33 cases per 100 thousand of population [1].

Its etiology and pathogenesis are still poorly understood. This disease can be triggered by viral infections, drugs that are structurally similar to the endogenous antigen within the epidermal-dermal junction. In such cases, an autoimmune

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response occurs when antibodies to an external hapten cross-react with an endogenous antigen. Drugs that can trigger an autoimmune response and stimulate the onset of cicatricial pemphigoid include local anti-glaucoma drugs, clonidine, and others. The main risk factor for the formation of skin vesicles (vesicular eruptions) is trauma (for example, eyelash epilation, chemical eye burns, prosthetics, and damage to oral mucosa with a toothbrush or other objects) [1, 2].

Clinical findings of pemphigoid include multiple organ damage, including eyes, the nasal cavity, skin and scalp, oral mucosa, pharynx, larynx and esophagus, anus, and genitalia. Conjunctiva involvement in the pathological process is extremely typical for cicatricial pemphigoid — it occurs in 64% of cases. This disease may begin with catarrhal conjunctivitis, hyperemia, conjunctival edema, soreness and photophobia; usually, it starts on one eye, and the second eye can subsequently be involved in the process. The name of this disease indicates the development of specific cicatrices. Vesicles and erosions develop on the conjunctiva; then, at the early stages, cicatrices can develop in the form of small adhesions between the conjunctiva and the eyeball or between the upper and lower eyelids. Later, coarse cicatrices form, leading to conjunctival deformity, symblepharon, ectropion, followed by trichiasis, corneal ulceration, clouding and its subsequent perforation with the loss of the iris. Due to the long course of this disease, the so-called "blind eye" is often observed when the cornea becomes completely covered with a cloudy membrane, allowing only the perception of light, leading to the disability of patients [2].

In cases of damage to the oral mucosa in the context of cicatricial pemphigoid, patients most often complain of bleeding gums when brushing teeth, and paresthesia; even mild chewing trauma can lead to desquamation. Gums, cheeks and the palate are involved in the pathological process; damage to the tongue and lower lip is somewhat less common. Blisters with serous or serous-hemorrhagic contents are formed on the oral mucosa, with a thick covering, surrounded by a hyperemic area; the blisters can persist for several days and usually open after trauma. In most cases, the blisters are arranged in groups and often recur in the same place, leading to cicatricial atrophy. Mucosal damage can result in adhesions, cicatrices in the pharynx, between the mucosa of cheeks and alveolar processes, in the corners of the mouth [3, 4].

In cases of nasal lesions, some patients can develop chronic atrophic rhinitis, synechias (fusion of the conchae with the nasal septum), which causes a sharp decrease in smell, difficult nasal breathing, and reduces the quality of life.

Limited skin lesions are observed in 24% of cases. Isolated blisters develop on unchanged skin or along with hyperemia on extremities or in skin folds. The blisters have a thick covering, and are persistent; erosions after said blisters heal slowly and with the formation of atrophic scars [4].

Granulomatosis with polyangiitis (GPA) refers to ANCA-associated (associated with anti-neutrophil cytoplasmic antibodies) systemic vasculitides that are characterized by the development of necrotizing granulomatous inflammation involving the respiratory tract and necrotizing vasculitis of small and medium-sized vessels [6]. As with cicatricial pemphigoid, oral and nasal mucosa is involved in the pathological process of GPA — ulcers develop, which subsequently results in nose deformation. The danger of GPA is renal damage with nephritis and renal failure. For cicatricial pemphigoid, eye damage is typical, which is included in the diagnosis criteria for this disease. GPA may also include damage to the organ of vision but primarily in the form of the orbital pseudotumor [5].

Therefore, clinical signs of GPA and cicatricial pemphigoid at a certain stage of the development of these diseases can be similar, contributing to the challenges in differential diagnosis. Although the management of both disorders involves glucocorticoids and cytostatics, dermatologists and ophthalmologists provide the primary care for cicatricial pemphigoid, while the diagnosis and treatment of systemic vasculitis is the task of rheumatologists.

We present the case report of a patient with differential diagnosis of GPA and cicatricial pemphigoid.

Case Report

Patient F., aged 60, was admitted to the Rheumatology Department of the Regional Clinical Hospital (Saratov) in August 2019 with complaints of pain in the right eyeball, lacrimation, nasal congestion, dry nose with bloody scabs, blisters on oral mucosa

with the formation of painful erosion when eating "irritating" food, long-term non-healing erosions on the skin of the lower extremities.

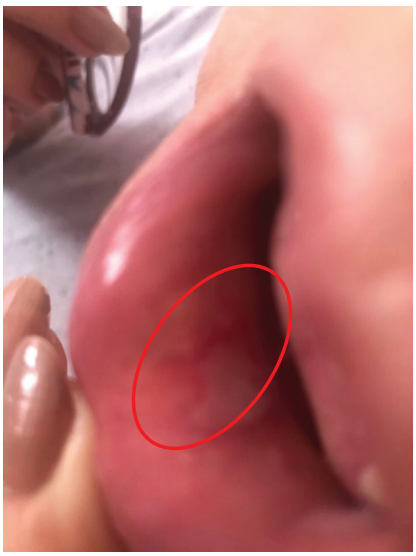
Disease onset was in 2016 when the patient first noticed gradually increasing nasal congestion. An otorhinolaryngologist diagnosed the patient with "atrophic rhinitis", local therapy was carried out without significant effect. A year after the first symptoms (in 2017), dry nose and bloody scabs occurred. The patient did not visit a physician, she was treated with local agents. In February 2018, a computed tomography (CT) scan of paranasal sinuses was performed; a left maxillary sinus cyst with a diameter of 1.6 cm was found, as well as moderate hyperplasia of the mucous membrane of maxillary sinuses of up to 0.2 cm. Examination by rheumatologist was recommended, but she did not consult this specialist.

In spring 2018, for the first time, the patient noticed vesicular elements on the oral mucosa; these later opened with the formation of ulcers. She visited a dentist and was diagnosed with aphthous stomatitis. Diet and oral treatment with potassium permanganate were prescribed, with a temporary positive effect and subsequent new erosions on the oral mucosa. In August 2018, a cytological test of the mucosa was carried out; neutrophilic leukocytes and structureless matter were found.

At the beginning of 2019, the patient began to notice long-term non-healing superficial erosions on the skin. In May 2019, she noticed vesicular elements in the right lower leg region. She visited a dermatologist at the place of residence; she was diagnosed with bullous pemphigoid. A single infusion of steroids was performed with a temporary positive effect. From 2018 to 2019, the patient lost more than 10 kg. A cancer screening test was carried out at a local clinic. In summer 2019, there was an episode of mumps, recurrence of aphthous stomatitis, with improvement after local therapy.

In July 2019, the patient experienced pain in right eyeball, photophobia, and lacrimation. She visited an ophthalmologist at the place of residence; topical nonsteroidal anti-inflammatory drugs (NSAIDs) in drops and antibacterial drugs were prescribed, without a significant effect. During re-examination by ophthalmologist, scraping of the upper eyelid mucosa was performed; granulations of the upper eyelid mucosa of the right eye were found; squamous metaplastic epithelium and large amounts of neutrophilic leukocytes were found in the scraping.

Examination by a rheumatologist was recommended. At the end of August 2019, the patient was hospitalized in the Rheumatology Department of the Regional Clinical Hospital (Saratov).



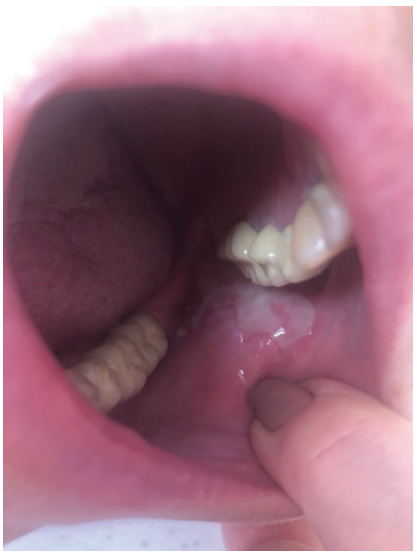


Figure 1. *Patient F. There are superficial ulcers from small erosions to confluent, up to 2-3 cm in diameter, covered with a white coating in the oral cavity on the mucous membrane of the palate, on the mucous membrane of the cheeks (in the projection of the molars)*

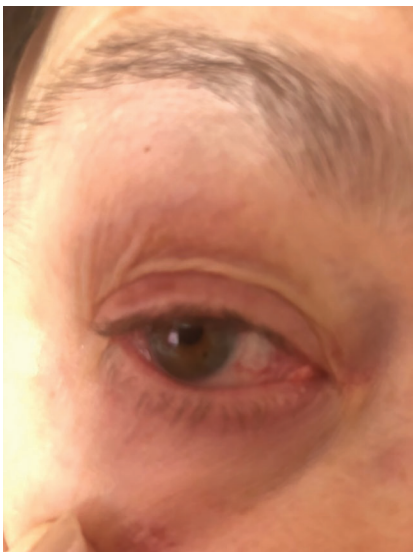


Figure 2. *Patient F. Hyperemia of the upper eyelid of the right eye*

The patient was examined for systemic pathology rather than for separate nosological units only three years after the disease onset.

During hospital examination, the following changes were revealed. Superficial ulcers from small erosions to confluent ones, with a diameter of up to 2–3 cm, covered with white plaque were found in the oral cavity, on the palatal mucosa, on the mucous membrane of the cheeks (in the projection of molars) (Figure 1). Hemorrhagic scabs, synechias, and significant narrowing of the lumen of nasal passages were found in the nasal cavity. Hyperemia of the upper eyelid of the right eye, photophobia and lacrimation were revealed (Figure 2). Isolated vesicular eruptions were found in the region of the right buttock, lower leg, and trunk.

Examination Results

Complete blood count showed slightly increased erythrocyte sedimentation rate (ESR); biochemical blood test showed slightly decreased total protein. Immunological test revealed antibodies (AB) to DNA in titer more than double the normal value. Common urinalysis within normal. Daily proteinuria — protein negative. Ultrasound examination (US) of kidneys: partial doubling of the right kidney; sinus cysts in the left kidney. Chest radiography revealed pneumosclerosis. Pathergy test was performed, the result was negative. Negative results of the cytological test (performed twice in history with an interval of 4 months) for acantholytic cells (oral mucosa, trunk) were obtained, which excluded pemphigus.

Considering lesions of the nasal cavity, ulcerative stomatitis, dermatitis, and the negative test for pemphigus, the following preliminary diagnosis was made: Granulomatosis with polyangiitis (probable), chronic — according to disease onset, grade II activity with upper respiratory tract damage (rhinitis, sinusitis), ulcerative stomatitis, visual impairment (granulation of upper eyelid OD), dermatitis, history of mumps.

The following treatment was prescribed: per os — prednisolone 30 mg/day, proton pump blocker (prevention of adverse gastric events), calcium agents.

Examination was continued.

CT of nasal sinuses: deviation of nasal septum; mucosa of nasal conchae, left 6 mm, right 4 mm; narrowed lumen of nasal cavity (at the level of inferior nasal concha); pneumatization of sinuses without changes.

CT of orbits — no abnormality found.

Examination by an ophthalmologist: granuloma of right upper eyelid, high degree hypermetropia; retinal angiopathy.

Examination by a dermatologist: considering the combined damage to mucous membranes of the oral cavity, nose, conjunctiva of the right eye, blisters in the oral cavity, long disease course, we cannot exclude the diagnosis of "cicatricial pemphigoid".

After obtaining the results of examinations and consultations with specialists, considering the combined lesions of the eyes, oral mucosa, skin, the narrowing of the nasal lumen, it was concluded that the patient probably has cicatricial pemphigoid. Granulomatosis with polyangiitis is doubtful since there is no typical lesion of ENT organs, kidney damage. Considering the disease activity, poor prognosis for the organ of vision, azathioprine (100 mg) was prescribed. It was recommended to continue taking prednisolone 30 mg/day, proton pump blocker, calcium agents. Repeated hospitalization was recommended after one month in order to monitor the efficacy and safety of treatment and to decide on the viability of biopsy of foci in the oral cavity.

During repeated hospitalization, the patient showed a negative result for anti-neutrophil cytoplasmic antibodies of the IgA class (ANCA). During treatment, there were no skin manifestations, damage to the oral mucosa, and the swelling of the right eye decreased.

Therefore, the diagnosis of cicatricial pemphigoid was established on the basis of the following criteria:

1. Typical symptoms (combined damage to eyes, mucous membrane of the oral cavity, skin, narrowing of the lumen of the nasal cavity).
2. Negative Nikolsky's sign.
3. No acantholytic cells (Tzanck cells) in the smear from the bottom of the erosion.

At the same time, the patient had no sufficient GPA criteria or signs of an oncological process.

Discussion

Systemic vasculitides are a fairly rare disorder (about 4.2 per 100 thousand of population per year). Usually, primary care physicians have difficulties in establishing this diagnosis. Visits to different specialists, with inefficacy or low-efficacy of the recommended therapy, multiple organ damage, presence of common signs of inflammation (weight loss, increased acute phase markers, etc.), suggest a systematic process; recommendations for examination by a rheumatologist were made. However, the systemic nature of signs does not always mean a systemic rheumatic disease; rarer diseases with characteristics similar to systemic vasculitides are sometimes found; careful assessment of diagnosis criteria and differential diagnosis are required. According to the literature and recommendations of dermatologists, vision loss is a criterion of cicatricial pemphigoid. In the present clinical observation, more than three years passed from the first signs of the disease to the diagnosis; repeated examinations by different specialists (dermatologist, ophthalmologist, dentist, rheumatologist) were performed. Establishing the diagnosis and prescribing treatment yielded a positive result with an expected favorable outcome while preserving the patient's vision. The rarity, little knowledge of this disease, and the lack of defined treatment standards make it necessary to expand its coverage in literature in order to improve diagnosis skills and facilitate timely and proper delivery of care to patients.

Author Contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

Magdeeva N.A. (ORCID ID: https://orcid.org/0000-0002-6397-3542): development of the concept and design, justification and writing of the manuscript, checking the content

Kobriseva A.A.: collection, analysis, interpretation of data, design of a review, writing a manuscript

Reznikova M.A.: concept development, collection of material, checking the content of the manuscript

Melekhina I.F.: collection, analysis and interpretation of data, content verification, final approval of the manuscript for publication

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