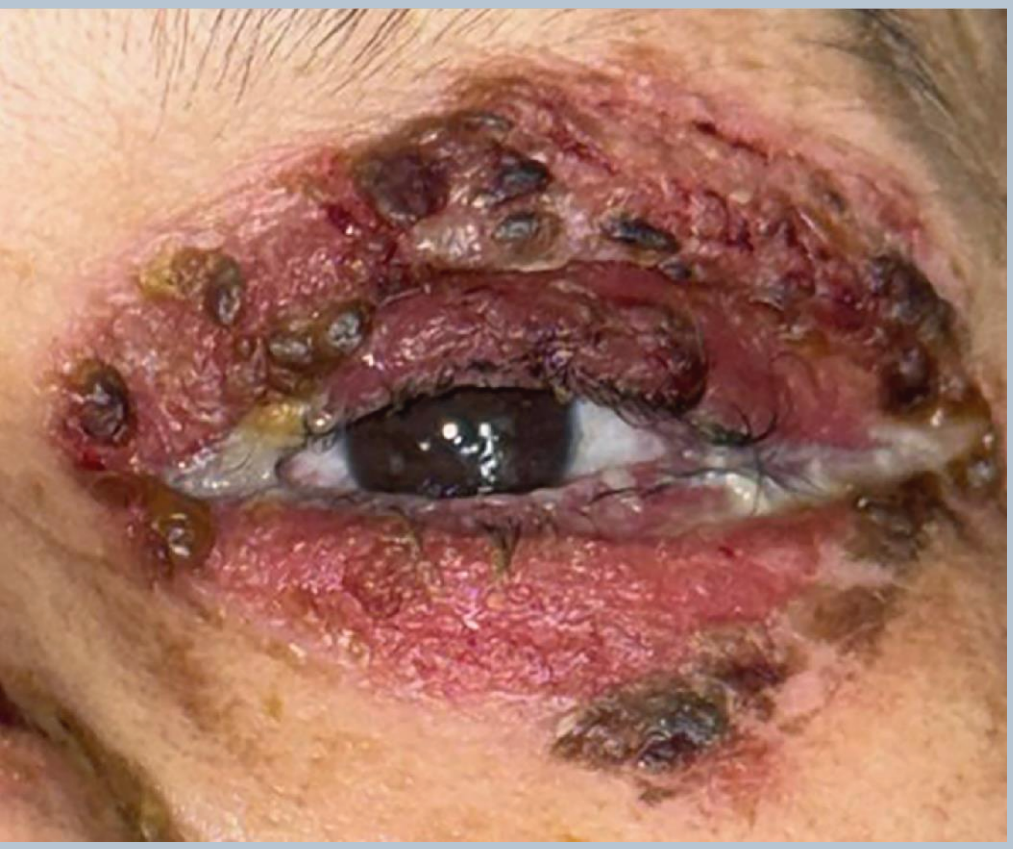
When Pemphigus Vulgaris Wreaks Havoc on the Ocular Surface: The Importance of a Multidisciplinary Approach



TROPHY CONTEST

Introduction:

Autoimmune bullous disorders (AIBDs) are a diverse group of immune-mediated dermatological pathologies, characterized by the appearance of various blistering lesions secondary to the loss of immune tolerance to endogenous skin proteins.[1] They may be further divided into two major groups: pemphigus, when the condition affects the epidermis, and pemphigoid, where autoimmune processes occur in the subdermis.[2,3]

Pemphigus vulgaris is a rare disease, with an average incidence of two cases per 100,000 inhabitants, yet it is the most common variant of pemphigus.[4] Its pathogenesis involves the formation of autoreactive IgG against desmosomes adhesion proteins, causing acantholysis and loss of cohesion between keratinocytes.[5] The best-identified targets are desmoglein-1, in the epidermis, and desmoglein-3, found in both skin and mucous membranes.[6]

Pemphigus vulgaris usually manifests between the ages of 40 and 60 years.[7] It slightly predominates in women, with a male-to-female ratio of 1:1.7.[8] However, in Mexico, the disease is even more common in women, showing a 1:4.4 ratio.[9]

The classic sign of this pathology is the presence of flaccid, non-pruritic, fragile blisters, that upon rupture leave moderate to highly painful erosions.[10] These typically appear in the oral mucosa but can occur in any mucosal portion of the digestive, respiratory, and genitourinary systems, or in the conjunctiva, as well as on any skin-covered area, with a predilection for the face, trunk, and interdigital spaces.[11] Depending on the lesion distribution, three variants have been described: predominantly mucosal, mucocutaneous, or solely cutaneous.[12]

Ocular manifestations are uncommon, reported in about 16.5% of cases[13], although it is believed that their actual prevalence is often underestimated due to the prominent oral and cutaneous symptoms.[14] Despite desmoglein-3 being present in all tissues of the ocular surface,[15] ophthalmic involvement is usually limited to the conjunctiva and ocular adnexa.[16] The main symptoms affecting the patient include tearing, foreign body sensation, red eye, and photophobia.[17,18] The most commonly reported signs are conjunctivitis and blepharitis, although cases associated with conjunctival masses, conjunctival scarring, ectropion, trichiasis, entropion, symblepharon, and ankyloblepharon have been reported in the literature.[13,15,19] Moreover, Tan and collaborators[20] reported that over 90% of patients with this disease exhibit manifestations associated with dry eye syndrome,such as decreased tear production, reduced tear break-up time, and positive staining with fluorescein.

The suspected diagnosis is primarily clinical, confirmed by the histopathological finding of intraepidermal acantholysis, and whenever possible, with immunofluorescence testing or enzyme-linked immunosorbent assay (ELISA).[21]

Once the diagnosis is confirmed, initial management should aim to induce remission through the use of corticosteroids and immunomodulators, in conjunction with symptomatic management.[22,23] It is worth noting that without appropriate treatment, the mortality rate ranges between 75-90%.[11,22]

Case Presentation:

This is a 49-year-old female patient who spontaneously presented to the emergency department and continuous admission unit of our medical center. During the initial triage evaluation, disseminated vesiculobullous lesions were found, as well as crusts from the drying of their contents. These lesions were not pruritic yet very painful, located on the trunk, neck, and perioral, perinasal, and periocular regions. A presumptive diagnosis of toxic epidermal necrolysis (TEN) was made. The continuous admission service requested a consultation from the dermatology department to confirm the presumptive diagnosis, and from the ophthalmology department to assess the integrity of the anterior segment.

Directed questioning revealed that the patient has no known chronic degenerative or ophthalmologic history, nor was she taking any medications. The patient reported that her current condition began approximately one month ago, as a generalized dermatosis of sudden and spontaneous onset on the trunk. After 15 days, periorificial lesions appeared. She reports having been previously diagnosed with a herpes zoster infection, treated with acyclovir, and with bullous impetigo, managed with azithromycin. On both occasions, there was no improvement, which led to her referral to our facility for comprehensive management.

During the ophthalmologic examination in the emergency department, the patient's visual acuity was measured with a near vision chart at 20/30, which did not improve with the use of a pinhole. Ocular reflexes were intact, and ocular movements showed no limitations.

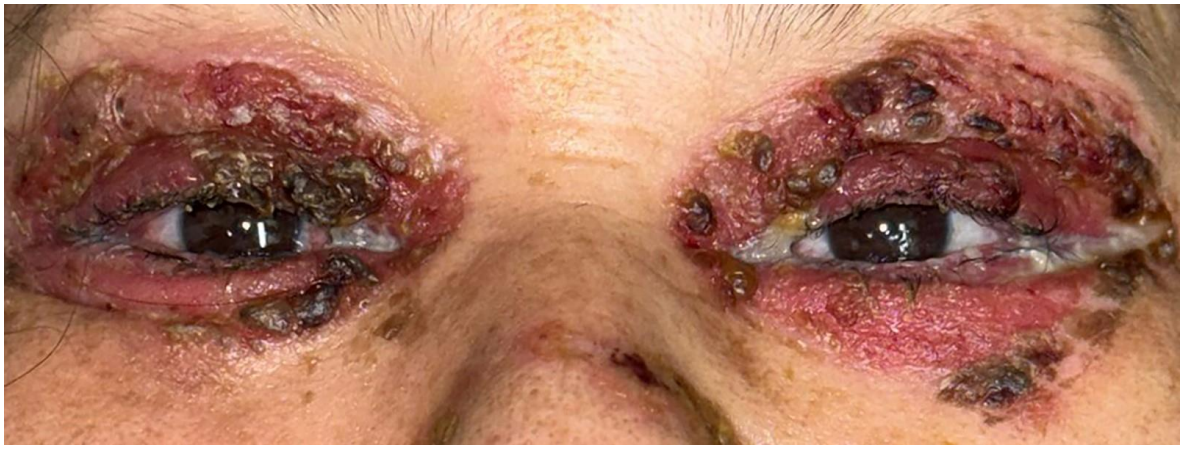


Figure 1: Clinical photograph showing extensive, ulcerative, and crusted lesions surrounding the eyelids and periocular area. There is evidence of conjunctival injection, discharge, as well as eyelid ptosis secondary to swollen eyelids.

The examination of the eyelids and adnexa reveals multiple vesiculobullous lesions with serous content, well-defined edges, friable, and painful to palpation, accompanied by crusts from the desiccation of the contents over the palpebral and periorbital areas bilaterally. These findings are associated with intense palpebral erythema, moderate palpebral edema, and whitish discharge on both palpebral margins bilaterally, with predominance on the lower borders. Additionally, collarettes and abundant remnants of discharge are observed at the base of the eyelashes.

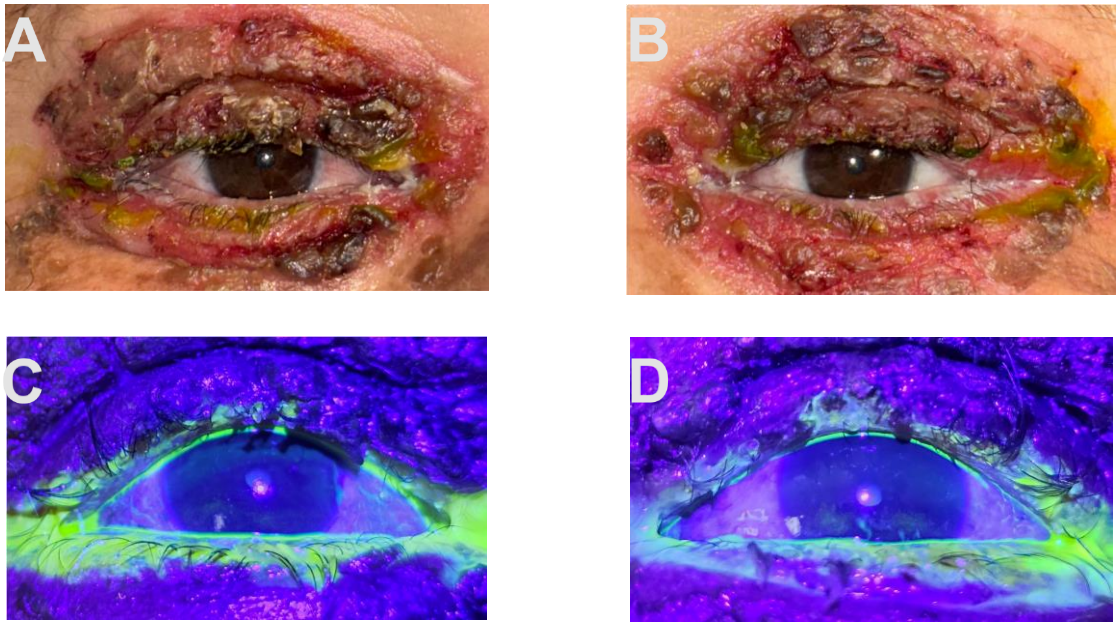


Figure 2: Color clinical photographs of the eyeballs and adnexa following fluorescein application. The upper images show right eye (A) and left eye (B) under white light, while the lower images show right eye (C) and left eye (D) under portable cobalt blue light. There´s remnants of discharge, and corneal involvement is clear, manifesting as punctate keratitis, both with a predominance in the left eye.

Macroscopically, the anterior segment shows moderate hyperemia of the bulbar conjunctiva in both eyes, without the ability to assess the tarsal conjunctiva or fornices due to intense pain upon manipulation. The tear break-up time is quantified at 5 seconds bilaterally. The cornea is transparent in both eyes. Fluorescein staining reveals moderate punctate keratopathy in the lower third of the cornea, with a predominance in the left eye. The rest of the ophthalmological examination yielded no data outside the physiological parameters.

Following the ophthalmological assessment, the diagnoses are integrated as follows:

- Bullous disease under study
- Blepharoconjunctivitis with probable bacterial superinfection
- Superficial punctate keratitis

For which the following management was established:

- Bilateral eyelid hygiene measures every 8 hours
- Gentle cleaning of secretions bilaterally as necessary
- Lubricating eye drops based on sodium hyaluronate every 4 hours in both eyes
- Dexpanthenol solutions every 12 hours in both eyes
- Tobramycin/dexamethasone ointment every 8 hours in both eyes

The dermatology service indicates that the lesions show a positive Nikolsky sign and a positive Asboe-Hansen sign, diagnosing bullous disease under study, likely cutaneous pemphigus vulgaris without mucosal involvement, and implementing the following management:

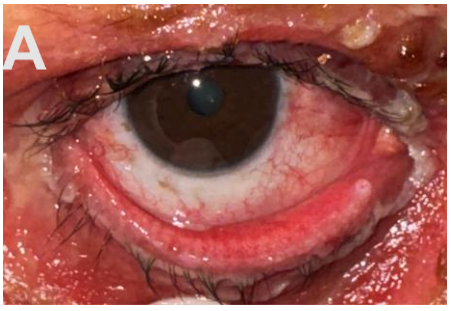
- Gentle cleaning and debridement of lesions
- Cream based on silver sulfadiazine every 12 hours immediately after lesion debridement

(promotes healing and has a prophylactic for superadded infection)

- Dressings with copper sulfate every 12 hours on lesions (used for its astringent activity, with secondary bactericidal and fungicidal activity)
- Ointment based on zinc oxide every 12 hours in the neck and groin regions (used for its astringent capacity)
- Prednisone tablets, 50 mg, every 24 hours orally
- Azathioprine tablets, 100 mg, every 24 hours orally
- The patient is admitted under their service for a confirmatory biopsy of the right leg, which is why the previously established treatment will be omitted in that region

Joint follow-up was conducted with the dermatology service throughout the patient's stay. Initially, daily assessments were performed and later every other day until discharge. Below is a summary of the patient's evolution during hospitalization:

- **Day 1:** Patient arrives. The continuous admission service requests systemic laboratory tests. The dermatology service requests cultures of samples obtained from mucosas in search of bacterial superinfection. The patient is diagnosed with a bullous disease under study, likely pemphigus vulgaris + blepharoconjunctivitis probably bacterial + superficial punctate keratitis.
- **Day 2:** A skin biopsy from the right calf is taken. Improvement in dermatological, ocular, and periorbital lesions begins to be observed; however, significant pain persists, limiting the patient's mobility enough to prevent them from performing basic activities. Thromboprophylaxis with enoxaparin is initiated, and oral analgesic management is started with acetaminophen and ketorolac. Results from the systemic laboratories requested by the continuous admission service are collected, finding all within normal parameters.
- **Day 3:** Continued improvement is noted; however, generalized pain persists, prompting a consultation with the pain management service, which suggests an analgesic regimen based on buprenorphine.
- **Day 4:** Continued improvement, with persistent generalized pain. The pain management service initiates a short-term regimen based on fentanyl.
- **Day 7:** Culture results are collected, finding no growth other than normal commensal mucosal microbiota. Biopsy results from the mid-third right calf reveal intraepidermal acantholysis compatible with pemphigus vulgaris. The patient has adequate analgesic control, allowing assessment of the tarsal conjunctiva and fornices. Additionally, a fundus examination is performed without finding alterations.



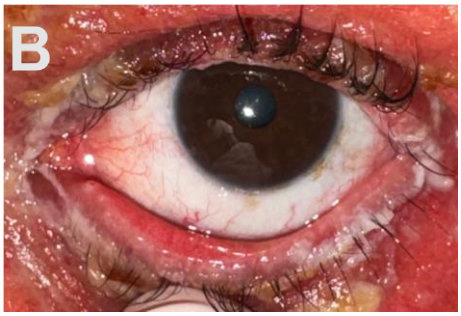


Figure 3: Color clinical photos of the right eye (A) and left eye (B) in which the evaluation of the tarsal conjunctiva and the fornices was achieved, 7 days after the start of treatment.

- **Day 8:** The patient achieves assisted ambulation with a family member. Minimal bullous lesions are observed, surrounded by adequate areas of denudation.
- **Day 10:** The patient is able to ambulate independently. Discharge is planned soon, and an oral analgesic regimen is progressed to evaluate pain prior to discharge.
- **Day 12:** The patient has adequate analgesic control with oral therapy and is capable of performing basic and instrumental activities of daily living independently; therefore, discharge is decided. Instructions are given to continue management at home by dermatology and ophthalmology. A follow-up appointment is scheduled in 10 days with both services.
- **Follow-up appointment after 10 days:** The patient does not attend the follow-up appointment with either dermatology or ophthalmology services. The reasons are unknown. Communication is attempted via telephone with the patient using the number provided upon admission; however, the telephone service reports that the number is not valid. The patient loses follow-up indefinitely.

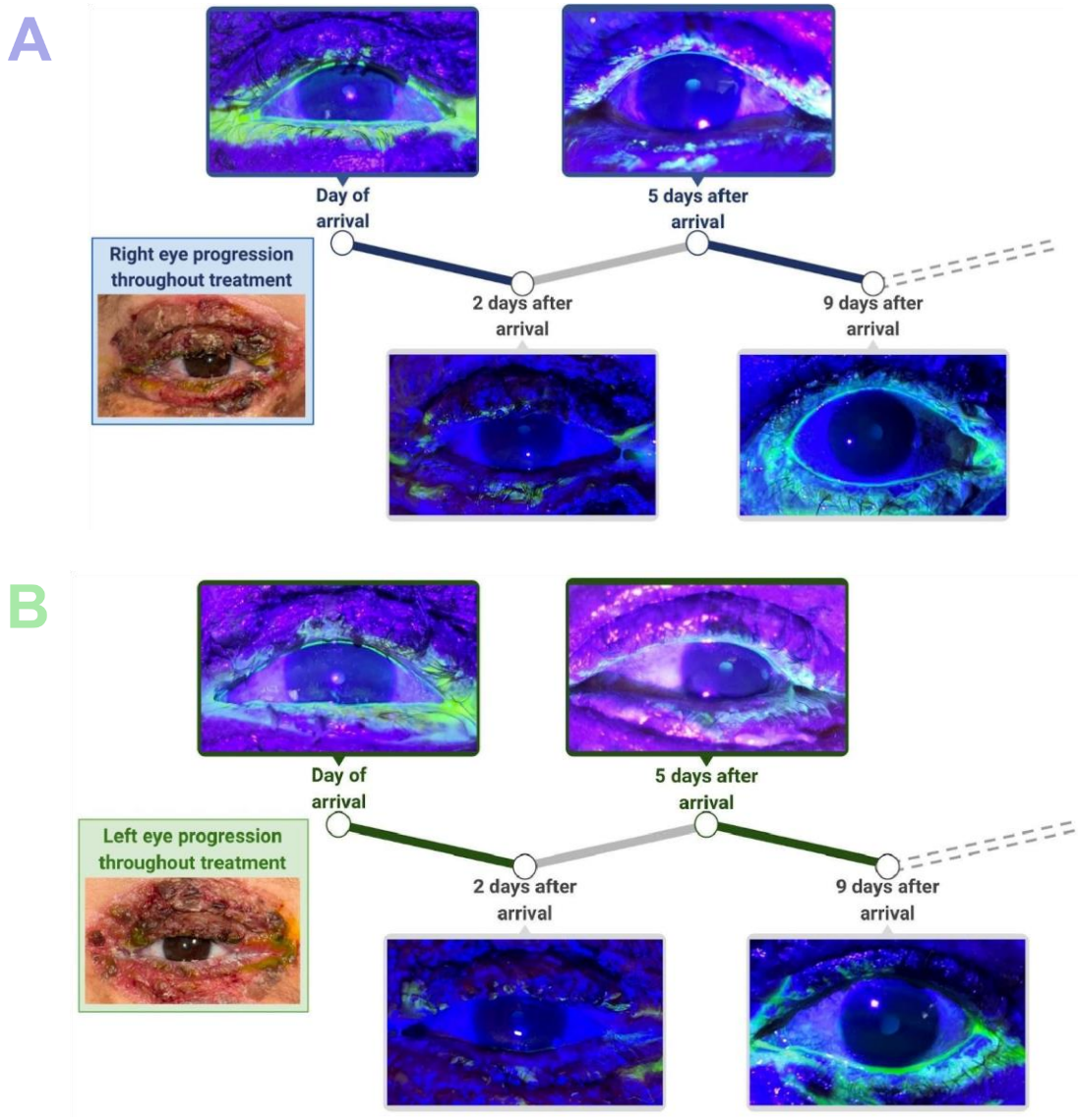


Figure 4: Progression and improvement of corneal involvement in the right eye (A) and left eye (B) over the days following the initiation of ophthalmological management.

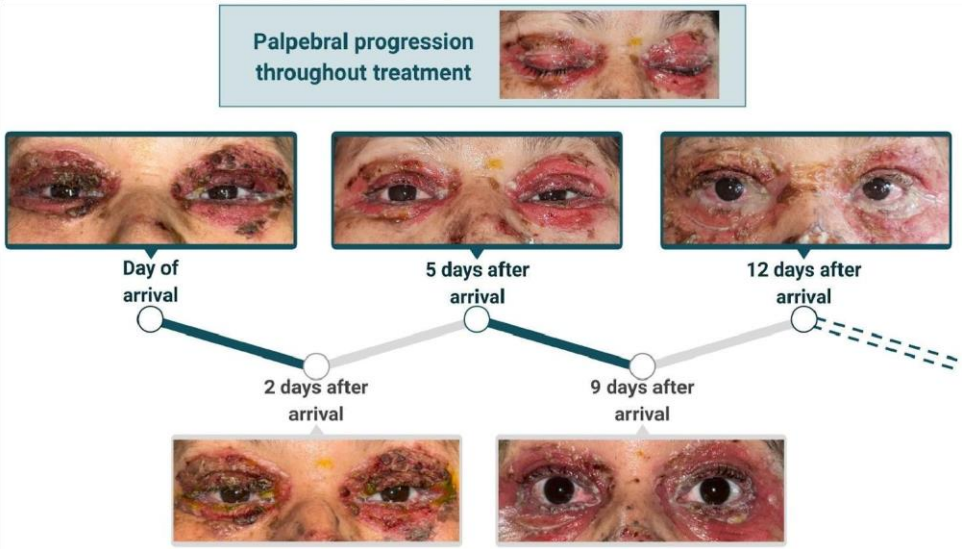


Figure 5: Progression and improvement of conjunctival and palpebral conditions in both eyes over the days following the implementation of ophthalmological management. The improvement of mechanical ptosis is quite evident after the resolution of palpebral edema.

Discussion:

Pemphigus vulgaris is a rare autoimmune condition that occasionally presents with ophthalmological manifestations. In the case of our patient, the variant with primarily cutaneous involvement was observed. Although the oral mucosa is the most common site of involvement in the majority of cases[6,24], the only mucous membrane affected in the patient was the conjunctiva.

This patient case also differs on the temporal relationship between the onset of the disease and the appearance of ophthalmological symptoms. Generally, ocular manifestations tend to appear several months or even years after the mucocutaneous debut[16,17], with dry eye syndrome and blepharoconjunctivitis being the most typical, as seen in our patient.

The management of pemphigus vulgaris is still not completely standardized due to the disease's low prevalence. The treatment primarily focuses on the use of corticosteroids (0.5-1.5 mg/day), which are effective in reducing the appearance of new blisters within 2 to 3 weeks, with complete remission expected around 8 weeks.[21,25] Additionally, immunosuppressants such as azathioprine (1-3 mg/day) and cyclophosphamide (100 mg/day) are used as corticosteroid-sparing agents, thereby limiting the risk of adverse effects associated with their use, while also increasing the disease-free interval.[23,26]

Although ophthalmological manifestations generally improve with adequate systemic management, supportive measures are recommended while achieving remission of the underlying disease.[15-18] Our treatment plan for the ocular surface alterations was proposed in

accordance with national[26] and international[27-29] consensus, suggesting the frequent use of preservative-free lubricants, dexpanthenol solutions, and antimicrobial ophthalmic ointments.

Unfortunately, the patient lost follow-up with our medical center after discharge, which is extremely risky, as the clinical course of pemphigus vulgaris is characterized by periods of exacerbation and remission, potentially leading to high mortality without continuous treatment. Complications may be directly related to the disease's pathophysiology, including obliterative bronchiolitis, gastrointestinal bleeding, and rheumatoid arthritis, as well as to the treatment used, which can cause Cushing's syndrome, hepatitis, bone marrow suppression, and an increased risk of infections and hematological neoplasms.[2,7,18] Regarding the ophthalmological complications associated with the disease and its management, cases of cicatricial conjunctivitis, ankyloblepharon, symblepharon, ectropion, scleritis, opacity, ulceration, and even corneal perforation have been reported.[15,30,31]

Mortality is primarily due to the severity of the dermatological involvement, which can lead to significant hydroelectrolytic disorders or disseminated infections, resulting in septic shock.[6,12]

Conclusions:

Pemphigus vulgaris is a rare and potentially serious autoimmune disease in which early diagnosis is essential to prevent severe and potentially fatal complications. Due to its low prevalence, it is unlikely that the ophthalmology trainee will have the opportunity to learn about this condition through direct clinical experiences, making the sharing of such cases in educational forums of utmost importance.

The previously discussed case highlights several crucial aspects that must be understood:

1. **Importance of Interdisciplinary Management:** Collaboration between dermatology and ophthalmology is essential to provide a comprehensive approach to the disease. Interaction between services allows for the identification of ocular alterations associated with the pathophysiology of the disease, which are often overlooked and underdiagnosed.
2. **Active Role of the Ophthalmologist:** The ophthalmologist should not limit themselves to making a diagnosis; they also have the responsibility to implement appropriate management that helps preserve the patient's ocular health while systemic treatment takes effect. This includes continuous monitoring and treatment of ocular symptoms to prevent deterioration.
3. **Awareness of Ocular Complications:** It is the ophthalmologist's responsibility to be aware of the serious ocular complications that can arise in patients with pemphigus vulgaris. Although these complications are uncommon, their potential to jeopardize the patient's vision and quality of life underscores the need for an adequate approach.

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