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Ocular cicatricial pemphigoid following Dipeptidyl Peptidase-4 inhibitor use: A case report

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ABSTRACT

Purpose: To report a rare Ocular Cicatricial Pemphigoid (OCP) case in a patient taking a Dipeptidyl Peptidase-4 Inhibitor (DPP-4 inhibitor), a medication used for the management of type 2 diabetes, for at least six years.

Observations: A 64-year-old male presented with refractory bilateral conjunctival inflammation and ocular discharge that had persisted for two months, despite multiple prior therapies for presumed bacterial conjunctivitis. Upon initial examination, clinical findings strongly suggested OCP, and he had elevated levels of anti-BP180 antibodies. Despite receiving systemic treatments such as steroid pulse therapy and therapeutic plasma exchange after discontinuing DPP-4 inhibitors, his condition progressively worsened, with manifestations such as forniceal shortening in his left eye. Consequently, the patient required keratoepithelioplasty, amniotic membrane transplantation in his left eye, and bilateral eyelid entropion surgery. His condition initially worsened for a time after discontinuing the DPP-4 inhibitor, but it gradually improved over time, and ocular surface surgical intervention was not required in the right eye.

Conclusions and Importance: The findings in this study demonstrate that severe refractory OCP may occur while taking the DPP-4 inhibitor, thus indicating that a detailed interview regarding medications is essential for patients with ocular pemphigoid, especially those with type 2 diabetes.

1. Introduction

Ocular cicatricial pemphigoid (OCP) is a form of mucous membrane pemphigoid (MMP) and chronic inflammatory ocular surface disease caused by antibodies against the mucosal epithelial basement membrane that causes severe conjunctival inflammation, conjunctival scarring with forniceal shortening, entropion, and trichiasis. Fibrosis of the ocular surface is known to cause symblepharon and forniceal shortening, resulting in severe dry eye.[1,2] The conjunctival invasion into the cornea due to limbal stem cell deficiency and dry eye due to aqueous tear deficiency and decrease of conjunctival goblet cells via ocular surface inflammation are observed, which may lead to permanent vision loss.[3] Acute exacerbation of this disease may be triggered by ocular surgery or infection.[4] It can also cause persistent epithelial defects in the cornea, resulting in significant corneal perforation. The diagnosis is established through clinical history and conjunctival biopsy.[5]

Dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors), which are known as gliptins, are oral diabetic medications that are commonly used for the treatment of type 2 diabetes mellitus.[5,6] DPP-4 inhibitors are generally considered safe and efficacy in general.[7] Many cases of bullous pemphigoid associated with DPP-4 inhibitors have been reported in recent years.[8] There is a case reports about the association between OCP and DPP-4 inhibitors in Japanese, but none in English.[9]

This report presents a rare case of severe OCP in a patient with type 2 diabetes mellitus treated with DPP-4 inhibitors for at least six years.

2. Case report

A 64-year-old man with a previous history of type 2 diabetes, dyslipidemia, and hypertension was referred to our hospital with a chief complaint of ocular discharge and conjunctival hyperemia in both eyes (Fig. 1). The previous doctor treated him for presumed bacterial conjunctivitis using several medications over a period of nearly two months, starting in February 2021. These medications included Chloramphenicol, Colistin sodium methanesulfonate, 0.1 % Betamethasone sodium phosphate, 0.1 % Ciclosporin eye drop, and 0.3 % Ofloxacin ointment.

In March 2021, upon initial presentation at our department, our

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examinations revealed that he had a conjunctival injection, limbal edema, symblepharon, trichiasis, and forniceal shortening. He had mild bilateral cataracts and the best-corrected visual acuity (BCVA) of 20/32 OD (oculus dexter/right eye) and 20/125 OS (oculus sinister/left eye). Bacterial cultures of the conjunctiva were performed at the time of the initial visit and no bacteria were detected in either eye. Clinical findings strongly suggested ocular cicatricial pemphigoid, so blood tests were performed, which were negative for Desmoglein-1 and 3 but showed mildly elevated anti-BP180 antibodies at 14.4 U/ml. An endoscopic examination performed by the department of otorhinolaryngology revealed erosions in the buccal mucosa, soft palate, nasal mucosa, epiglottis, and the posterior pharyngeal wall extending to the pharyngeal mucosa. We also noted that no skin lesions were observed. A detailed medication interview revealed that the patient was taking teneligliptin, a DPP-4 inhibitor.

The DPP-4 inhibitor was discontinued, and the patient was started on 60 mg prednisolone 34 days prior to the initiation of steroid pulse therapy. Additionally, 100 mg azathioprine was introduced 12 days prior to the commencement of steroid pulse therapy, both as part of the treatment for OCP. Despite initiating oral medications, his symptoms persisted. Therefore steroid pulse therapy, therapeutic plasma exchange, and intravenous immunoglobulin (IVIg) therapy were initiated. However, symblepharon and forniceal shortening progressed (Fig. 2). In February 2022, we performed keratoepithelioplasty and amniotic membrane transplantation to reconstruct the ocular surface, cataract surgery in the left eye, and bilateral eyelid entropion surgery for trichiasis. After surgery, in addition to continued oral prednisolone 16mg, 1.5 % levofloxacin eye drops, and 0.1 % betamethasone eye drops were initiated. After the initiation of prednisone by the dermatologist, starting at 60 mg/day, it was gradually tapered over time, and the patient remained on a maintenance dose of 16 mg/day of prednisone by the time of surgery. Thus, this treatment was not part of the perioperative management but a part of the ongoing management of the condition. We observed a significant improvement in the ocular surface and successful treatment for entropion and trichiasis (Fig. 2). In August 2022, the patient underwent eyelid surgery for recurrent left upper and lower entropion and right lower entropion, although there was no apparent worsening of the ocular surface. To manage the condition, the patient was prescribed 0.3 % gatifloxacin once daily in the left eye and 0.1 % betamethasone sodium phosphate once daily also in the left eye. In the right eye, the patient was administered chloramphenicol and colistin sodium methanesulfonate ophthalmic solution, along with 0.1 % fluorometholone, three times daily. Concurrently, the patient continued oral medications, including 12 mg of prednisolone and 100 mg of Azathioprine, as prescribed by the dermatologist. In January 2023, the ocular surface of the patient's left eye was stabilized, especially the findings in the right eye showing improved signs after discontinuing the DPP-4 inhibitor medication without any ocular surface reconstruction (Fig. 2). The best corrected visual acuity (BCVA) was 20/50 OD and counting fingers OS. There were no apparent exacerbations or adverse events at follow-up.

3. Discussion

Ocular cicatricial pemphigoid (OCP) is a rare and debilitating autoimmune disease that can lead to severe vision loss if not diagnosed and treated promptly. In this case report, we described a rare instance of severe OCP in a patient with type 2 diabetes mellitus who had been treated with a DPP-4 inhibitor for at least six years.

DPP-4 inhibitors are oral medications commonly used to treat type 2 diabetes mellitus due to their safety and efficacy. To our knowledge, there are no case reports in English on the association between OCP and DPP4 inhibitors.[9] However, several reports have suggested an association between DPP-4 inhibitors and bullous pemphigoid.[8,10] In Japan, in July 2023, the Pharmaceuticals and Medical Devices Agency issued a warning about pemphigoid associated with DPP-4 inhibitors (https://www.pmda.go.jp/files/000263415.pdf).

The exact mechanism by which DPP-4 inhibitors are associated with the development of bullous pemphigoid (BP) is not yet fully understood. Like the above, we believe that it is difficult to elucidate the mechanism of ocular cicatricial pemphigoid. However, some studies suggest that DPP-4 inhibitors may alter the antigenic properties of the skin, leading to the development of bullous pemphigoid. Considering the basic research report, a mouse study found that blocking DPP-4 led to eosinophils accumulating in the skin, a characteristic often seen in bullous pemphigoid (BP).[11] Like the infiltration of eosinophils into the skin in

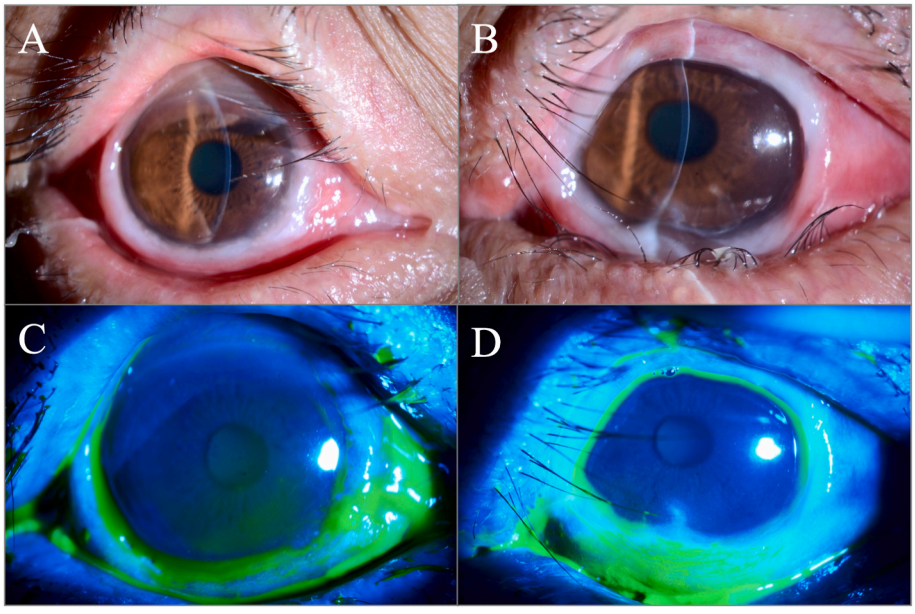

Fig. 1. Slit-lamp photographs of the patients at the time of the first visit without fluorescein (A–B) and with fluorescein (C–D). (A) Foster stage 3 symptoms in his right eye, including inferior fornix shortening, symblepharon formation, limbal edema, entropion, and trichiasis. (B) Foster has stage 3 symptoms in his left eye, including inferior fornix shortening, symblepharon formation, limbal edema, entropion, and trichiasis. (C, D) Photographs with fluorescein revealed corneal epithelial defects in both eyes.

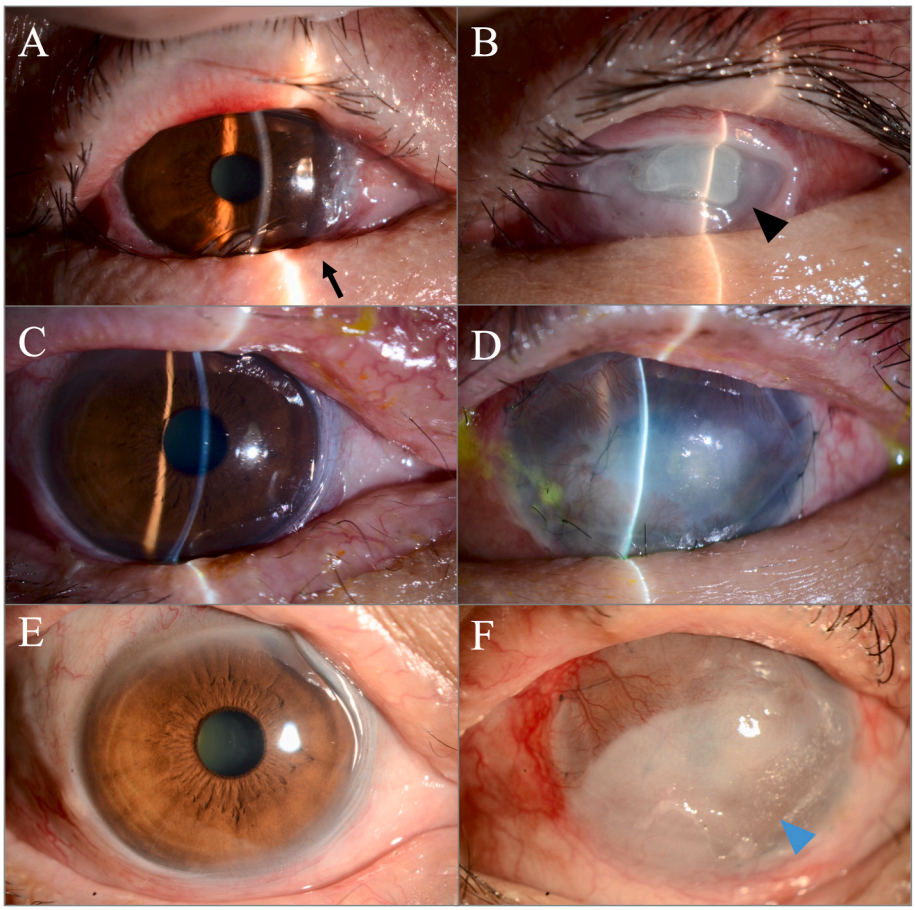

Fig. 2. Slit-lamp photographs were taken before surgery (A, B) and after surgery (C–F). (A) The right eye showed severe conjunctival inflammation and entropion (black arrow) preoperatively. (B) The left eye showed severe conjunctival inflammation, persistent epithelial defect, and calcium deposits (black arrow head) in the central cornea. (C) Slit-lamp photograph of the right eye at one month postoperatively. Correction of entropion is favorable. (D) Slit-lamp photograph of the left eye at one month postoperatively showed improvement in anterior eye inflammatory findings and forniceal shortening, and good correction of entropion. (E) Slit-lamp photograph of the right eye at 11 months postoperatively showed improvement in forniceal shortening and limbal edema without surgical intervention in the ocular surface, and inflammatory findings had subsided. (F) Slit-lamp photograph of the right eye at 11 months showed corneal keratinization (blue arrow head) and opacification, but the inflammatory findings and forniceal shortening had improved. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

this mouse model, we believe that eosinophil infiltration of the ocular surface under the influence of DPP-4 inhibitors may have contributed to the development of ocular pemphigoid. In addition to that, DPP-4, also recognized as lymphocyte cell surface protein CD26, serves a pivotal role in T-cell-mediated immunity. It is expressed on the membranes of various lymphocyte subtypes, including T, B, and NK cells, and plays a crucial role in modulating their cellular functions. It is known that the CD26 pathway might be triggered to boost immune responses for the treatment of cancer or chronic infection.[12] Recently, through genome-wide association studies (GWAS) and high-resolution HLA fine-mapping analyses, HLA-DQA1*5 has been identified as a significant genetic risk factor associated with bullous pemphigoid induced by DPP-4 inhibitors. Thus, we think that both the immunological roles of CD26 and the identified genetic risk factors collectively contribute to the pathogenesis of OCP.[13]

The elevation of the anti-BP180 antibody, one of the blood test features of OCP, was mild in this patient. In Japanese patients with DPP-4 inhibitors associated with bullous pemphigoid, anti-BP180 antibody titers have been reported to be negative or low in approximately 40–70 % of the cases.[8] We believe that OCP cannot be ruled out even if anti-BP180 antibody titers are low, and it is also essential to evaluate the accurate clinical presentation of the disease.

There still needs to be a test method that can prove the association between DPP-4 inhibitors and OCP. Hence, the possibility that OCP independently developed during DPP-4 inhibitor medication cannot be ruled out in this case. However, his clinical findings strongly suggest a possible link between OCP and DPP-4 inhibitors because the clinical results in the right eye improved after discontinuing the DPP-4 inhibitor.

Conjunctival biopsy with immunofluorescence is beneficial in OCP diagnosis confirmation, but surgical procedures may induce inflammation of the ocular surface, resulting in a rapid exacerbation of the disease and requiring caution. Even if a conjunctival biopsy is performed, it is reported to be negative in 20–40 % of patients with OCP.[14,15] Thus, a diagnosis based on clinical findings is essential, considering the risk of acute exacerbations by biopsy. In this case, a pathological examination of biopsied oral mucosal tissue was performed. The results were consistent with a diagnosis of mucous membrane pemphigoid, which supports our clinical diagnosis of OCP. However, the excised specimens were small and shrunk after excision, and specimens large enough for the immunostaining procedure were not obtained. Consequently, our diagnosis of OCP was not solely based on clinical findings. It was also strongly supported by the presence of anti-BP180 antibodies, which are often associated with pemphigoid diseases.

In a French study of approximately 210,000 adverse drug reactions, the reported odds ratio for bullous pemphigoid was as high as 67.5 for DPP-4 inhibitors.[16] The exact mechanism of bullous pemphigoid occurring during DPP-4 inhibitor therapy is still unknown, but increased inflammatory cytokines or involvement in immune tolerance have been

suggested.[17] In recent years, DPP-4 inhibitors have been reported to be associated with bullous pemphigoid and mucous membrane pemphigoid.[18] Thus, it is possible that OCP, a subtype of mucous membrane pemphigoid, may develop due to DPP-4 inhibitors administration.

In this case, the clinical findings improved with the discontinuation of DPP-4 inhibitors. This case highlights the importance of a detailed medication history for patients with ocular pemphigoid, especially those with type 2 diabetes. Physicians should be vigilant for any signs of OCP in patients receiving DPP-4 inhibitors and promptly discontinue the medication if a connection is suspected. Early recognition and intervention are crucial to minimizing the risk of permanent vision loss and other complications associated with OCP.

In summary, we presented the development of severe OCP during DPP-4 inhibitor medication. Some patients diagnosed with OCP may have developed this disease due to DPP-4 inhibitors, although no similar reports exist. Further studies are needed to establish a definitive link and investigate the underlying mechanisms involved in this potential association. In the meantime, healthcare providers should consider this possible relationship when managing patients with ocular pemphigoid and type 2 diabetes and be prepared to adjust treatment plans accordingly. Hence, we hope this case report clarifies the pathogenesis of OCP in the future.

In conclusion, in the case of ocular pemphigoid in type 2 diabetic patients, DPP-4 inhibitors may cause OCP and require a detailed medical history and appropriate treatment changes.

3.1. Patient consent

Consent to publish this case report has been obtained from the patient in writing. This case report does not contain any personally identifying information.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Author contributions

HF, CS, NY and AY established the clinical diagnosis and managed patient care. HF, CS and AM conceptualized the manuscript. AM, HF and CS equally contributed to drafting, writing, and editing the manuscript. All authors collaboratively developed and approved the manuscript, as well as verified the data.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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