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A case of IgG4-related conjunctival tumor with severe systemic allergy treated with antibodies against cytokine receptors

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ABSTRACT

Purpose: To present a case of IgG4-related conjunctival tumor in which anti-IL-5 receptor alpha-chain and anti-IL-4 receptor alpha-chain antibodies were administered for eosinophil sinusitis and severe bronchial asthma, but conjunctivitis could not be controlled.

Observations: A 53-year-old male patient started to receive anti-IL-5 receptor alpha chain antibody to treat eosinophilic sinusitis and eosinophilic severe bronchial asthma. Several months later, proliferative changes of the right palpebral conjunctiva appeared and were treated with tacrolimus and betamethasone eye drops. However, the findings gradually worsened and the right upper palpebral conjunctiva remained exposed. Exposed tissue was resected and histopathological examinations revealed the presence of IgG4 positive cells (10>/400HPF). Anti-IL-5 receptor alpha chain antibody treatment was stopped and changed to prednisolone. The findings improved and anti-IL-4 receptor alpha chain antibody was added to control eosinophilic sinusitis and eosinophilic severe bronchial asthma. The lesions worsened when the prednisolone was reduced under treatment with anti-IL-4 receptor alpha-chain antibody.

Conclusions and importance: In this case, the proliferative changes could not be suppressed by treatment targeting IL-5R receptor alpha-chain and IL-4R receptor alpha-chain, suggesting that the patient had VKC-like severe allergic conjunctivitis as a manifestation of IgG4-related disease. Additionally, it should be noted that if the severe conjunctivitis cannot be suppressed by treatment with immunosuppressive eye drops or various systemic biological agents, the conjunctivitis may be a manifestation of IgG4 related disease.

1. Introduction

Severe allergic conjunctivitis represented by vernal keratoconjunctivitis is a typical inflammatory disease in which proliferative changes are observed in the upper tarsal conjunctiva. As a disease other than allergy, ligneous conjunctivitis, in which abnormal serum plasminogen is involved, is known. In recent years, IgG4-related disease, in which tumor formation accompanied by fibrosis is observed in various tissues throughout the body due to the accumulation of IgG4-secreting cells, has attracted attention. Thus, when proliferative changes are observed in the conjunctiva, it is necessary to consider various pathological conditions such as vernal keratoconjunctivitis, ligneous conjunctivitis, and IgG4-related conjunctivitis.

2. Case presentation

In September 20XX, a 53-year-old male patient was diagnosed with eosinophilic sinusitis and eosinophilic severe bronchial asthma, and blood eosinophil count was high in the 20–70% range, therefore, treatment with anti-IL-5 receptor alpha chain antibody (Benralizumab, 30mg subcutaneously every 4 weeks)[1] was started in January 2019. The patient had conjunctival hyperemia before the start of treatment, but became aware of itching and ocular seborrhea around December 2018. In June 2019, the patient visited a nearby doctor, who pointed out conjunctival proliferative changes and referred to our clinic (Fig. 1). The patient was diagnosed as severe allergic conjunctivitis resembling vernal keratoconjunctivitis (VKC) and started treatment with 0.1% tacrolimus eye drops twice a day and 0.1% betamethasone phosphate eye drops six times per day. Corneal epithelial disorder was mild. The treatment was self-interrupted. In December 2019, the right upper palpebral conjunctiva remained exposed (Fig. 2) and the patient was not able to return the eyelid to the original position, and therefore, the patient returned to our clinic on December 25, 20XX+1. The right upper palpebral conjunctiva was surgically resected on February 4, 20XX+2 and proceeded for

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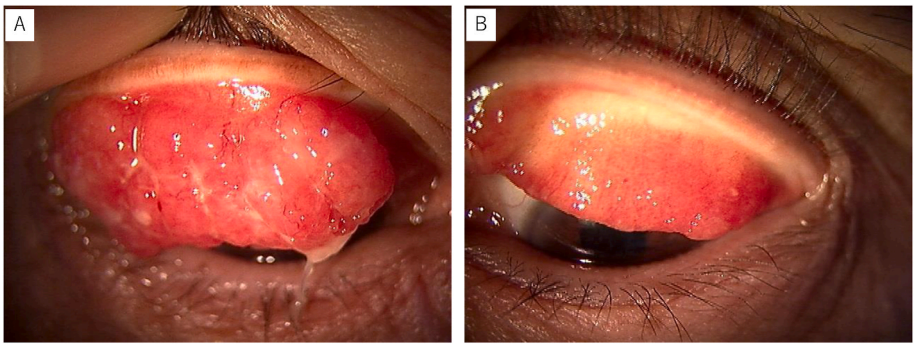

Fig. 1. Slit photographs at the initial visit (June 2019). A: right eye, B: left eye.

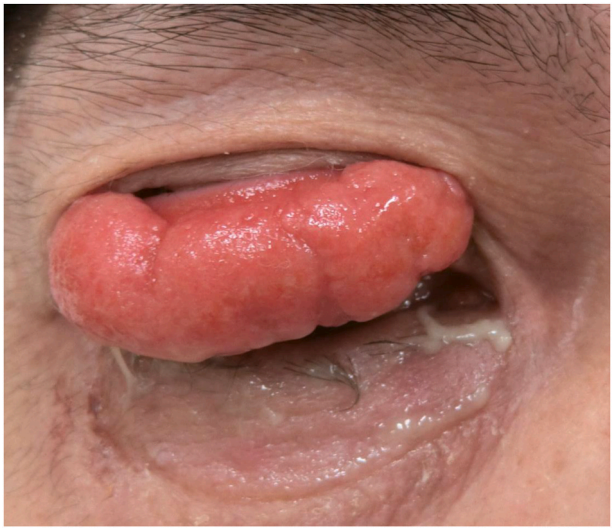

Fig. 2. Photographs of the right upper palpebral conjunctiva (January 2020). Note that the right upper palpebral conjunctiva remained exposed.

histopathological examination. The pathological diagnosis was pyogenic granuloma of the palpebrae (Fig. 3A). Immunostaining revealed the presence of CD3 positive T cells (Fig. 3B), CD79 positive B cells (Fig. 3C), IgG positive plasma cells (Fig. 3D). Furthermore, subclass evaluation showed IgG4 positive cells (Figs. 3E and 10>/400HPF) and IgG4 positive cells/IgG positive cells ratio more than 40% (Fig. 3D and E). In March 20XX+2, the left upper palpebral conjunctiva became exposed, and on March 15, 20XX+2, a left palpebral conjunctiva was surgically resected. In April 20XX+2, blood sampling confirmed an increase in serum IgG4 to 244 mg/dl, and a diagnosis of IgG4-related[2] conjunctival tumor was made, because histopathologic diagnosis was not confirmed in other tissues. As for asthma, treatment with anti-IL-5 receptor alpha chain antibody was discontinued in May 20XX+2, and since then, the patient has been treated with oral prednisolone 30 mg/day for one month and conjunctival proliferative changes and hyperemia were suppressed. In June 20XX+3, anti-IL-4 receptor alpha-chain antibody (Dupilumab, 300mg subcutaneously every 2 weeks) therapy[3] was added at a dose of 8 mg/day prednisolone. Subsequently, worsening of conjunctival proliferative changes was observed again, so the dose of prednisolone was increased to 10 mg/day while anti-IL-4 receptor alpha-chain antibody therapy was continued. Thereafter, conjunctival proliferative changes and hyperemia were suppressed.

3. Discussion and conclusions

To the best of our knowledge, there are no reports of VKC-like findings in patients with eosinophilic sinusitis and severe bronchial asthma prescribed biological agents. Other upper tarsal conjunctiva proliferative entities should be considered in the differential diagnosis such as ligneous conjunctivitis.[4] Serum level of α2 plasmin inhibitor/plasmin complex[5] was below 0.3 μg/ml, suggesting that ligneous conjunctivitis is less likely. Angiolymphoid hyperplasia with eosinophilia (ALHE) should also be excluded because conjunctival inflammation and eosinophilia. Indeed, a case of angiolymphoid hyperplasia with eosinophilia accompanying vernal conjunctivitis was reported previously.[6] However, the clinical finding in the case was an erythematous mass of the right bulbar conjunctiva and was completely different from our case (tarsal conjunctival proliferative changes).

It is unclear how anti-IL-5 receptor alpha-chain antibodies are involved in pathogenesis of progressive proliferative changes of the palpebral conjunctiva. The patient was mildly relieved by prednisolone, but the lesions worsened when the prednisolone was reduced under treatment with anti-IL-4 receptor alpha-chain antibody. Thus, in this case, the proliferative changes could not be suppressed by treatment targeting IL-5 receptor alpha-chain and IL-4 receptor alpha-chain. These facts suggest that IL-5R alpha-chain and IL-4 receptor alpha-chain are less likely involved in the development of upper tarsal conjunctival proliferative changes. Furthermore, increase of predonisolone dose improved upper tarsal conjunctival proliferative changes suggests that activation of IgG4-producing cells was suppressed by predonisolone. Taken altogether, the patient had VKC-like findings in the conjunctiva as a manifestation of IgG4-related disease. The possibility of IgG4-related syndrome should be kept in mind when patients present with intense conjunctivitis that cannot be suppressed by treatment with immunosuppressive eye drops or various systemic biological agents.

Patient consent

Written consent to publish this case has been obtained.

Funding

None.

Authorship

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

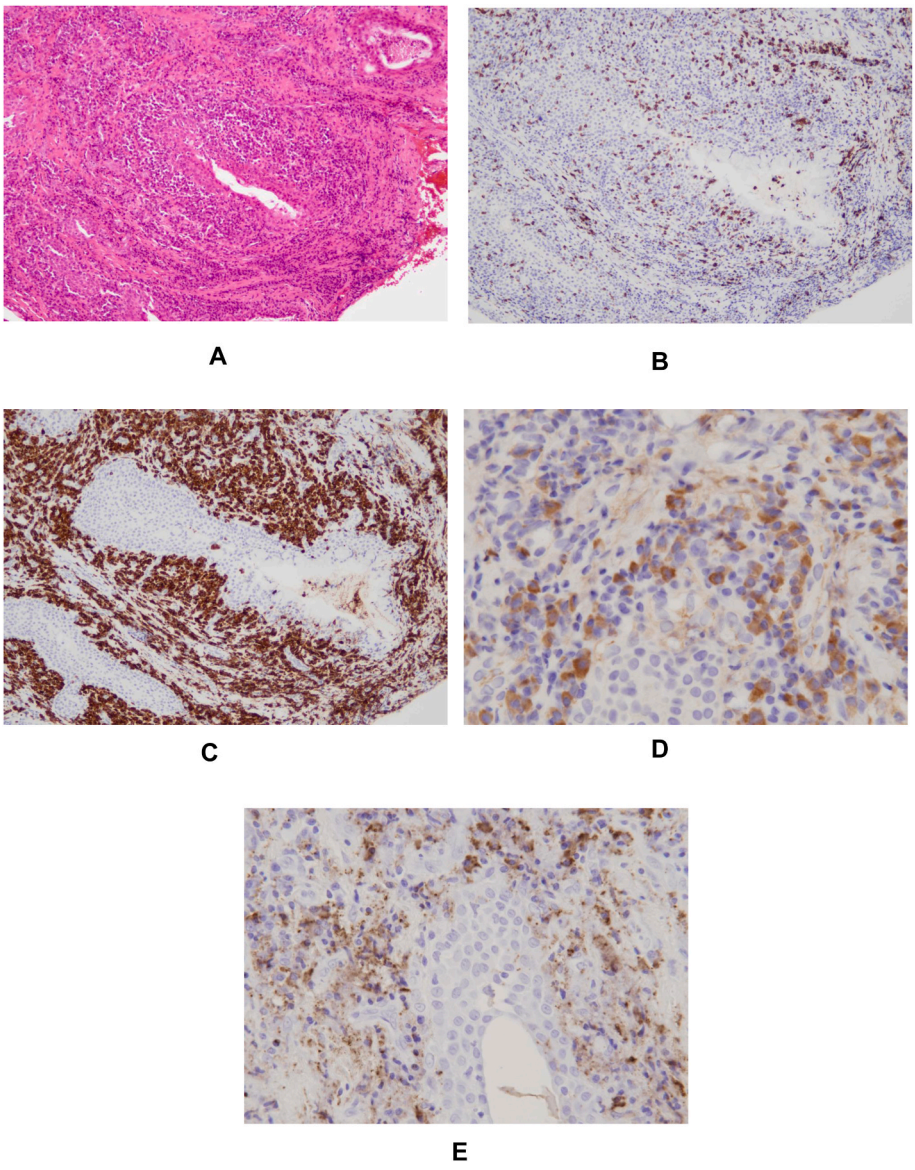

Fig. 3. Photographs of histopathological examinations for the surgically resected right upper palpebral conjunctiva (February 2021). A: HE staining, x40, B: anti-CD3 immunohistochemistry, x100, C: anti-CD79a immunohistochemistry, x100, D: anti-IgG immunohistochemistry, x400, E: anti-IgG4 immunohistochemistry, x400.

Declaration of competing interest

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