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The Overlap Syndrome: A Case Report of Chronic Graft-Versus-Host Disease After the Development of a Pseudomembrane

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Background: Ocular graft-versus-host disease (GVHD) is one of the most severe complications of hematopoietic stem cell transplantation. It manifests as an impairment of the ocular surface, such as severe dry eye disease, and deteriorates the recipient's visual function and quality of life. We encountered an "overlap syndrome" of ocular GVHD, which is characterized by the presence of both acute and chronic GVHD symptoms. In this report, we present the treatment progress of the overlap syndrome in a case with ocular GVHD.

Case Presentation: A 57-year-old man with acute myeloblastic leukemia underwent hematopoietic stem cell transplantation. Six weeks after the treatment, the recipient complained of eye pain and discharge. He was diagnosed with the overlap syndrome due to low tear volume, severe corneal epithelitis, hyperemia, and a pseudomembrane on the conjunctiva. Immune cells infiltration, fibrinoid degeneration, fibroblastic and spindle-shaped cells, and fibrosis were observed in the pathology of the pseudomembrane. The recipient was treated with topical immunosuppression and pseudomembrane removal. One week after the initial treatment, ocular GVHD improved. Twelve weeks after the treatment, the topical steroid was discontinued due to the elevation of intraocular pressure.

Conclusions: The assessment of conjunctival pseudomembrane in ocular GVHD is important to determine the stage of the case and to assess systemic GVHD. Furthermore, prompt removal of the pseudomembrane after diagnosis is an appropriate management to reduce the symptoms of ocular GVHD. The combination of topical steroids and immunosuppressive agents is suggested to be an effective treatment in management of overlap syndrome.

Key Words: graft-versus-host disease, dry eye disease, overlap syndrome, pseudomembrane, tacrolimus

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Graft-versus-host disease (GVHD) is a lethal complication of hematopoietic stem cell transplantation (HSCT). Eyes are one of the organs being affected, which can manifest as ocular GVHD.[1] Ocular GVHD is characterized by severe dry eye disease (DED), keratoconjunctivitis sicca, pseudomembrane formation, meibomian gland dysfunction, and conjunctival fibrosis. In severe cases, it might lead to filamentous keratitis, a shield ulcer, and corneal perforation, which could be dangerous to recipients' visual function.[1–3] More than half of the recipients of HSCT develop ocular GVHD,[4,5] but mechanism-specific treatment has not yet been established.

Traditionally, GVHD was classified according to the period when the symptoms of GVHD first appeared after HSCT: acute GVHD if symptoms appeared before 100 days and chronic GVHD if symptoms appeared after 100 days.[6] Recently, the clinical signs and pathological findings[7,8] were reclassified. Chronic GVHD was reclassified as a combination of traditional chronic GVHD and 1 or more acute GVHD

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Consent for Publication: Based on the requirement of the institutional ethical review board of Keio University School of Medicine, written informed consent was acquired in this case report. This report does not contain any personal information that could lead to the patient's identification.

Availability of data and materials: Data sharing is not applicable to this case report.

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symptoms, also called the overlap syndrome. Several cases of systemic findings of the overlap syndrome have been reported. However, ocular findings are rarely reported.[6] In the overlap syndrome, acute GVHD symptoms occur in the chronic GVHD phase of recipients' conjunctiva. Thus, ocular progress in the overlap syndrome is important because a similar development might be recognized in the whole mucosal tissue such as in the intestine, oral, and skin.

For systemic GVHD, the administration of systemic immunosuppressants is the main treatment. However, the first-line treatment of ocular GVHD is topical steroids, which could also have several side effects. The essential role of T cells in the pathophysiology of GVHD is well known.[1,9] Therefore, topical immunosuppressants in ocular GVHD will be a suitable treatment according to this mechanism and a promising strategy to reduce inflammation and dryness in ocular chronic GVHD.[10] In this case report, we describe a case of overlap syndrome in the eyes, which manifested after the development of a pseudomembrane and was treated with topical immunosuppressants.

CASE PRESENTATION

A 57-year-old Asian man with acute myeloblastic leukemia underwent peripheral blood stem cell transplantation. Before the transplantation, the patient was referred by the Division of Hematology, Department of Internal Medicine, Keio University Hospital, for pre-HSCT DED screening. The patient had no significant ocular history and no use of any eye drops, including antibiotics in the past 6 months. The values of the Schirmer test were 15 and 5 mm (right eye and left eye, respectively), and the corneoconjunctival lissamine green (LG) staining score was 0 of 9 points. The corneal fluorescein staining (CFS) score was 1 of 9 points, and the intraocular pressure (IOP) was 14.0 and 16.0 mm Hg (right eye and left eye, respectively). There were no other abnormal findings of the cornea through the retina. In addition, his blood test findings showed negative results for the cytomegalovirus antibody. After the procedure of HSCT, methotrexate and cyclosporine were administered systemically. The drug concentration was set between 450 and 550 ng/mL. These prophylaxes were tapered with the time course. However, during the emergence of acute plus chronic GVHD, patients receive systemic steroid administration (refer to the detail further).

Twenty-six days after HSCT, the patient presented with oral ulcers (Fig. 1A), rashes (Fig. 1B) in the whole body, and diarrhea. Therefore, he was diagnosed with acute GVHD. Forty-two days after HSCT, he complained of pain and discharge in both eyes and was then referred to the Department of Ophthalmology. The Schirmer's test score was 5 and 3 mm (right eye and left eye, respectively). Other test results were as follows: LG staining score, 5 of 9 points; CFS score, 8 of 9 points; the degree of hyperemia, 2 of 2 points; ocular surface disease index, 50 points; tear-film breakup time, 1 second; and the severity score as proposed by the International Chronic Ocular GVHD Consensus Group proposed ICO score), 11 of 11 points (Figs. 2A–C).[11] Moreover, broad pseudomembrane and symblepharon were observed in both eyes. Thus, we diagnosed the patient with overlap syndrome of acute and chronic GVHD.

As a primary treatment, the pseudomembrane was removed, and topical betamethasone and tacrolimus were started 4 times a day. The pathology of the pseudomembrane showed infiltration of immune cells, fibrinoid degeneration, a colony of fibroblastic and spindle-shaped cells, and slight fibrosis in damaged epithelia (Fig. 3B). In addition, infiltration of $CD68^+$ macrophages was observed (Figs. 3C, D). $CD4^+$ T cells were seen more than $CD8^+$ T cells (Figs. 3E, F).

Seven days after the initial treatment (56 days from HSCT), the value of the LG staining score was 3 of 9 points, the CFS score was 2 of 9 points, and the total ICO score improved to 7 of 11 points (Figs. 2D, E). Dosage of the topical steroid and the immunosuppressive agent was tapered. After that, the ocular symptoms slightly worsened throughout the reduction of systemic steroid treatment (day 112, Fig. 2F). Dosage of topical betamethasone and tacrolimus was decreased to 3 times per day. At 147 days after HSCT, IOP became elevated up to 28 and 19mm Hg (right eye and left eye, respectively). This elevation was due to the frequent use of topical steroids. Therefore, topical betamethasone was discontinued, and tacrolimus eye drops were increased to 4 times a day. After discontinuation of topical steroid treatment, IOP decreased to normal range (14 mm Hg). Subsequently, the subjective and objective ocular symptoms and the ICO score were controlled by topical tacrolimus only.

In addition, symptoms of acute GVHD in the skin and gut were treated by topical betamethasone and oral budesonide. Systemic immunosuppression was continued by the systemic administration of prednisolone 60 mg per day (1 mg/kg) and then tapered (up to 272 days from HSCT). Because this description is the same as that described in the previous cases (reported by Dr. Miki Uchino), it is better to describe that dry eye was observed at the same time as the onset of pseudomembrane.

DISCUSSION

We encountered a case of chronic GVHD with the development of a pseudomembrane. The pathology of a pseudomembrane commonly shows infiltration of mature T cells from the donor graft to the recipient's conjunctival epithelia. These epithelial cells degenerate into the pseudomembrane. After that, macrophages infiltrate as scavengers to phagocytose the degenerated epithelia, as shown in Figure 3. A greater number of macrophages, $CD8^+$ T cells, $CD4^+$ T cells, and fibroblastic cells infiltrated the degenerated epithelia simultaneously (Fig. 3).

Infiltration of macrophages into conjunctival epithelia at an early stage after HSCT, in this case, could be a sign of acute ocular GVHD, as seen in acute cutaneous GVHD.[12] Infiltration of fibroblastic cells in the same region and the rapid progression of fibrosis of conjunctiva were likely signs of chronic ocular GVHD.[13] Therefore, this case could be an overlap syndrome in the ocular surface.

It has been reported that a large amount of cytokine release from infiltrated macrophages and the ocular surface is exposed to cytokine storm,[13] which leads to corneal ulcer.[14]

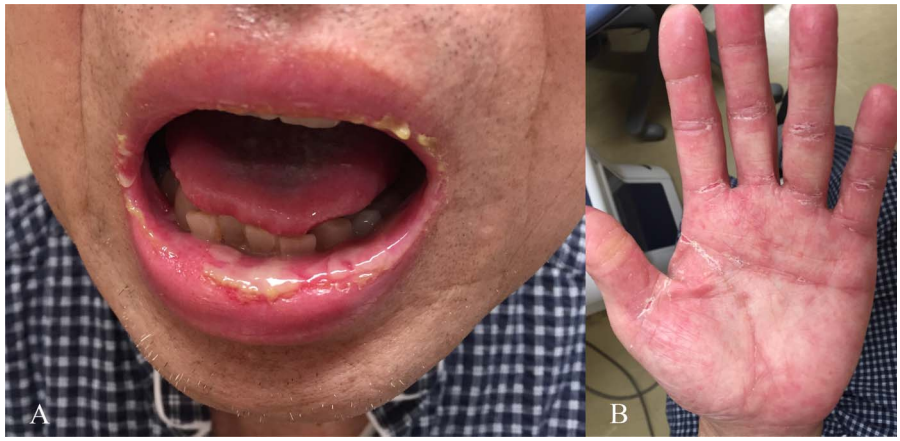

FIGURE 1. Findings of systemic graft-versus-host disease: oral ulcers (A) and generalized skin rash (B) were observed. (The full color version of this figure is available at www.corneajrnl.com.)

Moreover, pathological fibrosis presumably developed by chemokines such as stromal-derived factor 1[15] stimulates the infiltration of the fibroblast that are released from the pseudomembrane. We hypothesized that this phenomenon leads to spontaneous punctual occlusion,[16] meibomian gland dysfunction,[14] and conjunctival fibrosis.[17] Thus, the removal of the pseudomembrane was the key to control the cytokine storm and resist the progression of ocular GVHD in this case report.

There is a mucosa-associated lymphoid tissue in conjunctiva, which is also associated with gut-associated lymphoid tissue.[18] The pseudomembrane in the gut causes diarrhea, which is the main symptom of gut GVHD. Moreover, it erupts into a wide range of symptoms that influence recipients' vital progress. It has been reported that life expectancy is worse in cases of conjunctival GVHD.[19] Hence, the observation seen in conjunctiva could be correlated with the progress in the gut. It is important to have close contact between the Ophthalmology and Hematology departments.

For systemic diagnosis of the case, the patient had skin and gut symptoms as acute GVHD findings. Moreover, oral ulcers and DED were the reasons for chronic GVHD diagnosis. Therefore, the case was diagnosed as overlap syndrome. The systemic and ocular courses were both treated with appropriate systemic and topical immunosuppressants.

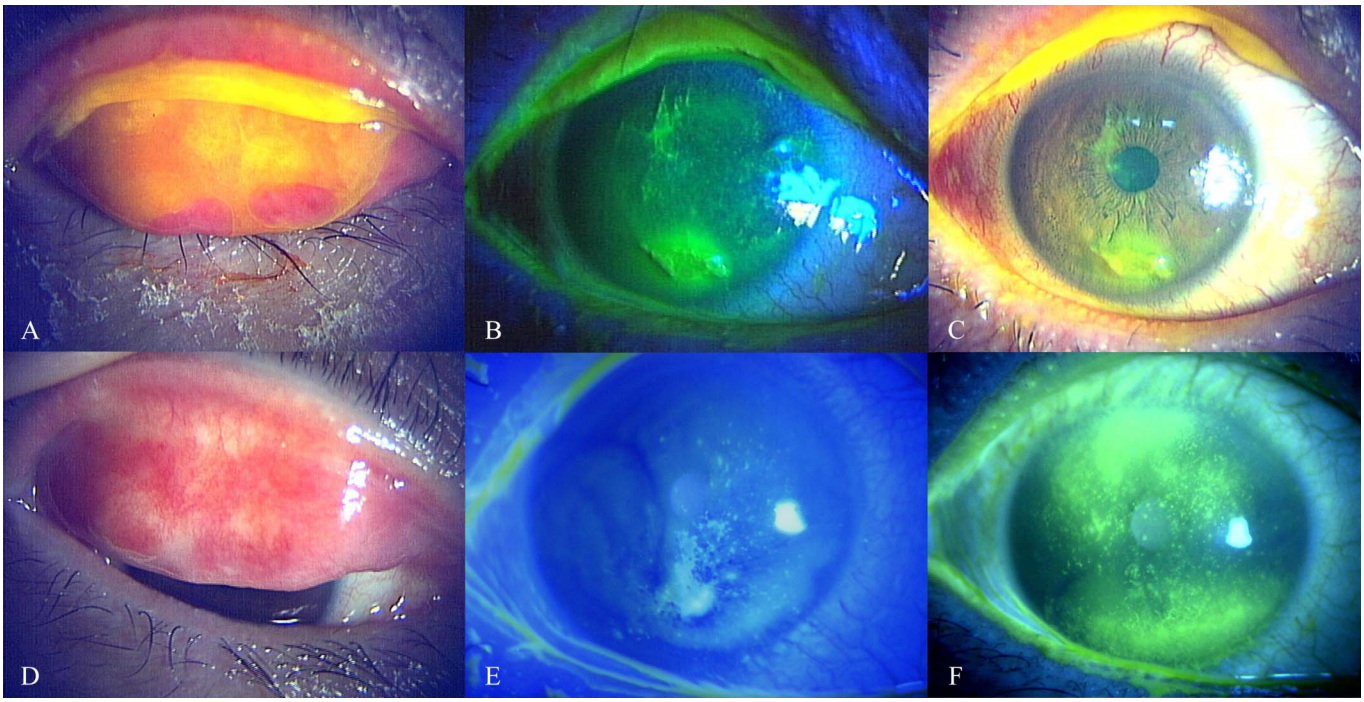

FIGURE 2. Ocular graft-versus-host disease. Ocular findings at 42 days after hematopoietic stem cell transplantation: pseudomembrane (A), short tear-film breakup time, and severe corneal plus conjunctival epithelial defect (B, C) were observed. D and E, After 7 days from initial treatment (day 56). F, Exacerbation of the ocular graft-versus-host disease after reduction of systemic steroid treatment (day 112). (The full color version of this figure is available at www.corneajrnl.com.)

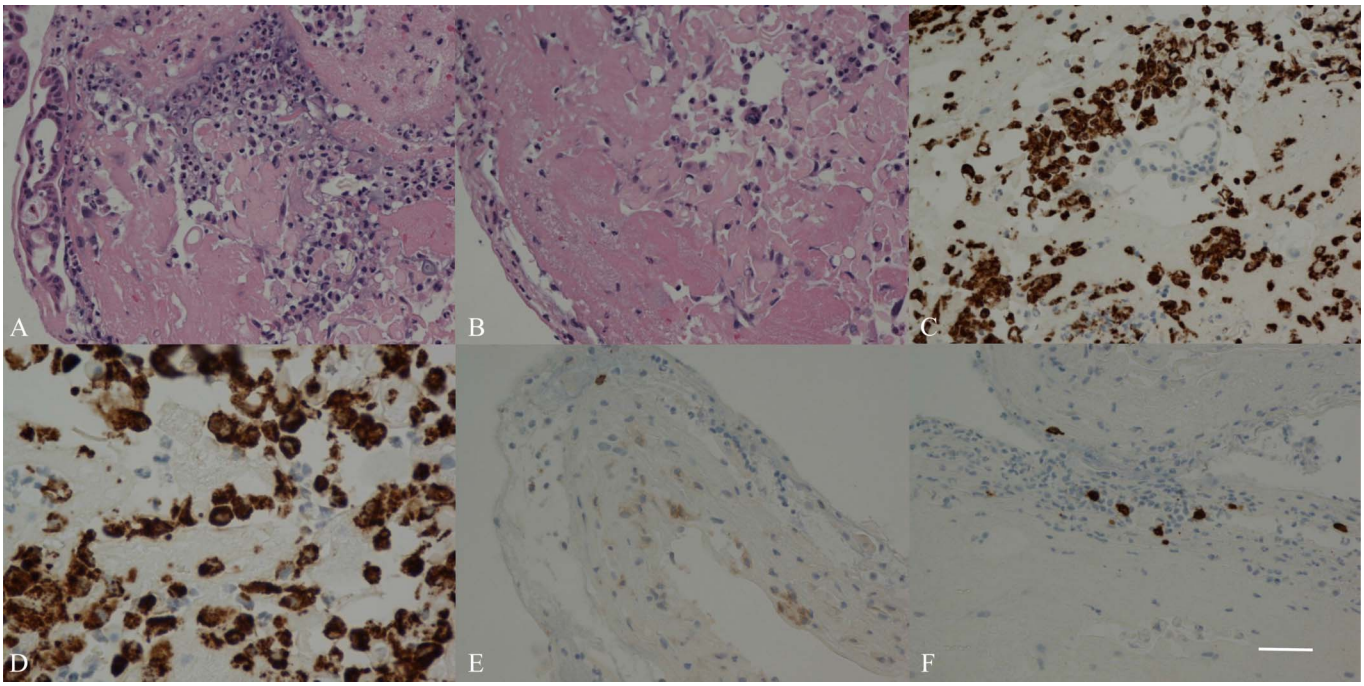

FIGURE 3. Pathology of the pseudomembrane. A and B, Hematoxylin and eosin staining of the pseudomembrane: infiltration of immune cells, fibrinoid degeneration, a colony of fibroblastic and spindle-shaped cells, and slight fibrosis were observed. C and D, Diaminobentizin staining of the pseudomembrane. Infiltration of $CD68^+$ macrophages and $CD4^+/8^+$ T cells was observed (E, F). (The full color version of this figure is available at www.corneajrnl.com.)

Presence of the pseudomembrane is suggested to be the findings in acute GVHD so that the removal of the pseudomembrane in the conjunctiva could be sufficient for the additional treatment.

This case presented with the most severe form of ocular GVHD, as represented by the ocular GVHD severity score (Fig. 2). The combination of topical steroids and immunosuppressive agents was the treatment of choice. Donor T cells play a role in pathophysiology of acute GVHD.[20] The combination of symptoms of acute and chronic GVHD, for example, $CD4^+$ and $CD8^+$ T cells in the pseudomembrane, suggests that the selection of topical tacrolimus was effective. However, the topical steroid had to be discontinued due to the elevation of IOP. Despite the termination of topical steroids, ocular symptoms still stabilized. Treatment of this case could be evidence that topical immunosuppression is effective in addressing the pathophysiology of ocular GVHD. Side effects of topical steroids include cataracts, glaucoma, infection, and delayed wound healing. In addition, long-term complications of HSCT are cataract (6.8%–14.0%)[4,21] and glaucoma (15.0%).[22] Therefore, the long-term use of topical steroids in patients who underwent HSCT could worsen the quality of vision. Thus, we believe that topical immunosuppression might be one of the options in ocular GVHD treatment.

Two previous reports have demonstrated occurrences only in children: a child with pseudomembrane after cord blood transplantation[13] and another child with pseudomembrane with overlap syndrome.[8] However, to the best of our knowledge, this is the first case to report overlap syndrome that appears with the development of a pseudomembrane in an adult recipient.

To summarize our case report, the assessment of the conjunctival pseudomembrane in the case of GVHD is important to determine the stage of the case and to assess systemic GVHD. Furthermore, the removal of the pseudomembrane is an appropriate management for reducing the symptoms of ocular GVHD. The combination of topical steroids and immunosuppressive agents is an effective treatment of overlap syndrome in ocular GVHD.

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