

# Crohn's disease-associated keratopathy: A case report

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## ABSTRACT

**Purpose:** This study reports a case of Crohn's disease-associated keratopathy that progressed with disease activity. **Observations:** A 29-year-old man diagnosed with Crohn's disease and receiving systemic adalimumab therapy, presented with an irregular epithelial surface, superior corneal opacity, subepithelial infiltration, pannus with new vessel ingrowth, and punctate epithelial erosions in both corneas. Changes in ophthalmological findings were checked during regular outpatient follow-ups. We also compared the stool calprotectin values obtained at a gastrointestinal clinic during the course of keratopathy. By analyzing the trend of fecal calprotectin levels in this patient, we found that keratopathy worsened as fecal calprotectin levels increased. Corneal neovascularization and infiltration improved as the fecal calprotectin levels decreased.

**Conclusions and importance:** The mechanism of Crohn's disease-associated keratopathy has not been identified but appears to be related to the autoimmune mechanism of Crohn's disease. Managing Crohn's activity by referring to the gastroenterology department should be considered to relieve Crohn's disease-associated keratopathy.

## 1. Introduction

Crohn's disease is a representative inflammatory bowel disease (IBD) associated with autoimmune mechanisms.<sup>1</sup> It is well known that Crohn's disease can cause iritis and uveitis,<sup>2</sup> which is reflected in the Crohn's disease activity index criteria.<sup>3</sup> However, cases of Crohn's disease-associated keratopathy have been rarely reported worldwide. In 1980, the first case of keratopathy associated with Crohn's disease was reported.<sup>4</sup> Bilateral corneal subepithelial infiltration was the predominant finding in this case, and this finding has also been reported in other rare cases of Crohn's disease-associated keratopathy.<sup>5</sup> We present another case of Crohn's disease-associated keratopathy that progressed along with Crohn's disease.

## 2. Case report

A 29-year-old man visited the outpatient clinic with a recurrent appearance of hyperemia in the left eye that had started 7 months prior. He was diagnosed with Crohn's disease following an endoscopic examination and biopsy conducted in the gastroenterology department 3 years ago. Treatment was with adalimumab therapy since the first

diagnosis at the gastroenterology department. The patient had no remarkable ophthalmological history. At the first visit in June 2020, his visual acuity was 20/20 in both eyes. The intraocular pressure and fundus examination results were within normal limits in both eyes. An irregular epithelial surface and punctate epithelial erosion on the cornea were found in the left eye (Fig. 1A and B), and the right eye was normal. The Sjogren's International Collaborative Clinical Alliance ocular staining score of the left eye was equivalent to 4 points.<sup>6</sup> Cyclosporin A 0.1 % eye drop twice a day and frequent artificial tears were used in both eyes; however, there was no significant improvement. Three months after the first visit (September 2020), corneal neovascularization and pannus appeared in both eyes (Fig. 1C and D). Loteprednol etabonate 0.5 % thrice a day was added. Six months after the first visit (December 2020), as the above findings worsened with subepithelial corneal infiltration and new superior corneal opacity (Fig. 2), the topical loteprednol dose was increased to six times daily, and autologous serum 20 % eye drop six times a day was added. Ten months after the first visit, the course appeared to gradually improve, particularly in the right eye. However, starting in October 2021 (18 months after the first visit), corneal neovascularization increased again, and in December 2021, it worsened, even in the right eye (Fig. 3A and B). We analyzed the trend in

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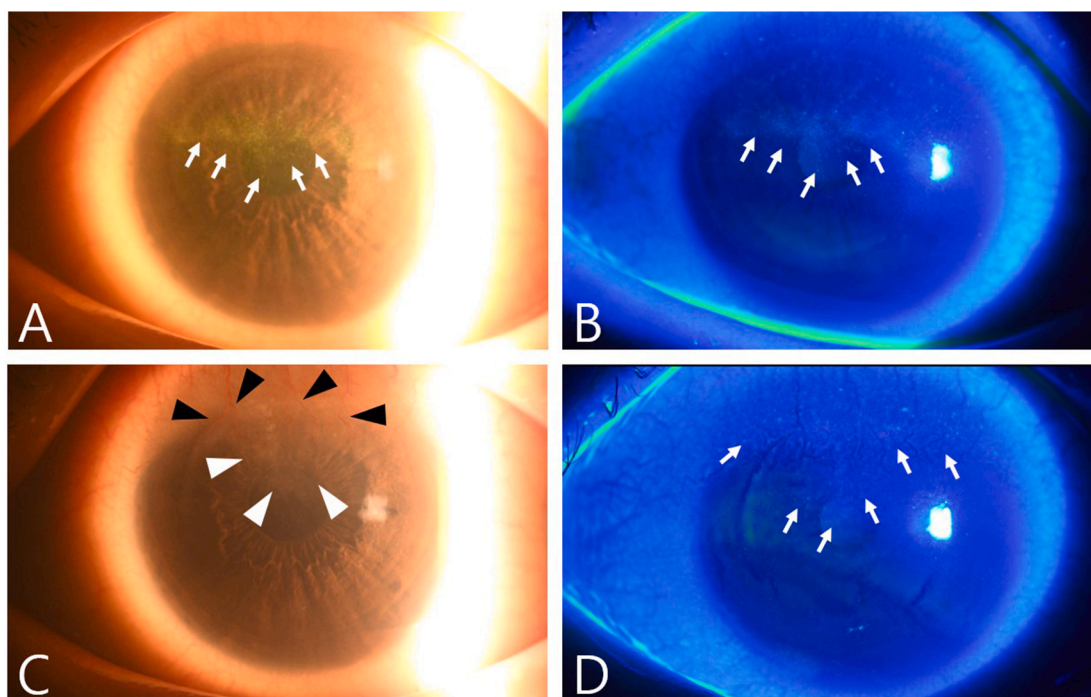
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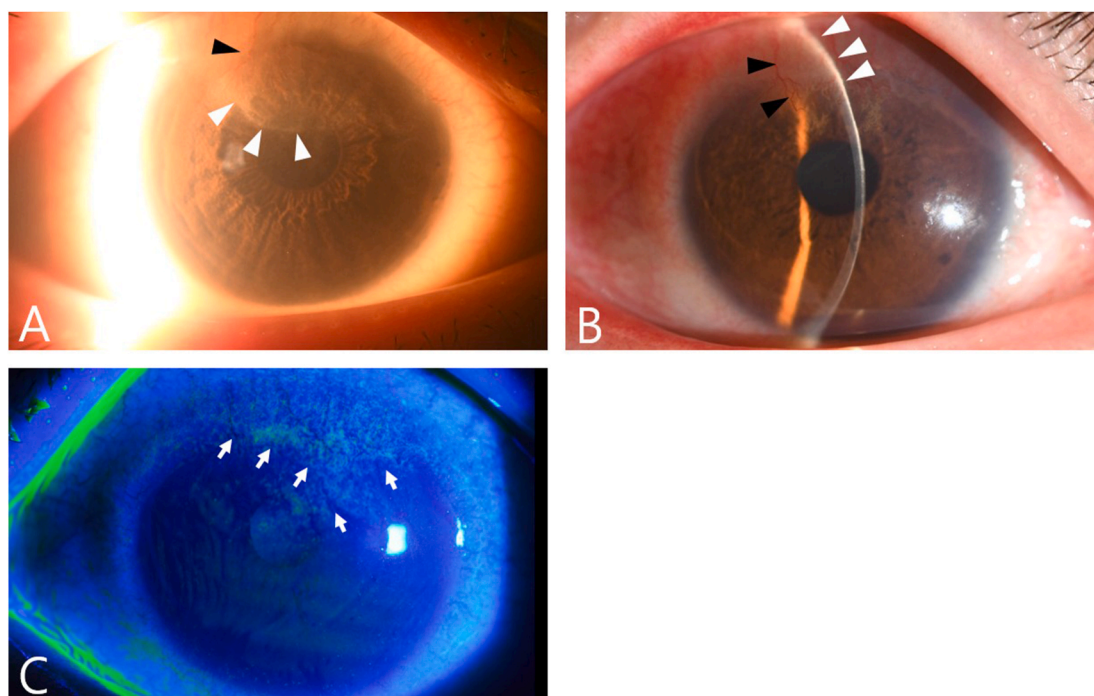
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**Fig. 1.** A-B, slit-lamp photograph on the first visit (June 2020). Irregular epithelial surface and punctate epithelial erosion (white arrow) are shown (A, B). C-D, slit-lamp photograph 3 months after the first visit (September 2020). Corneal neovascularization (black arrowhead) and pannus (white arrowhead) are shown (C). Irregular epithelial surface is also clearly shown on fluorescein staining (D).

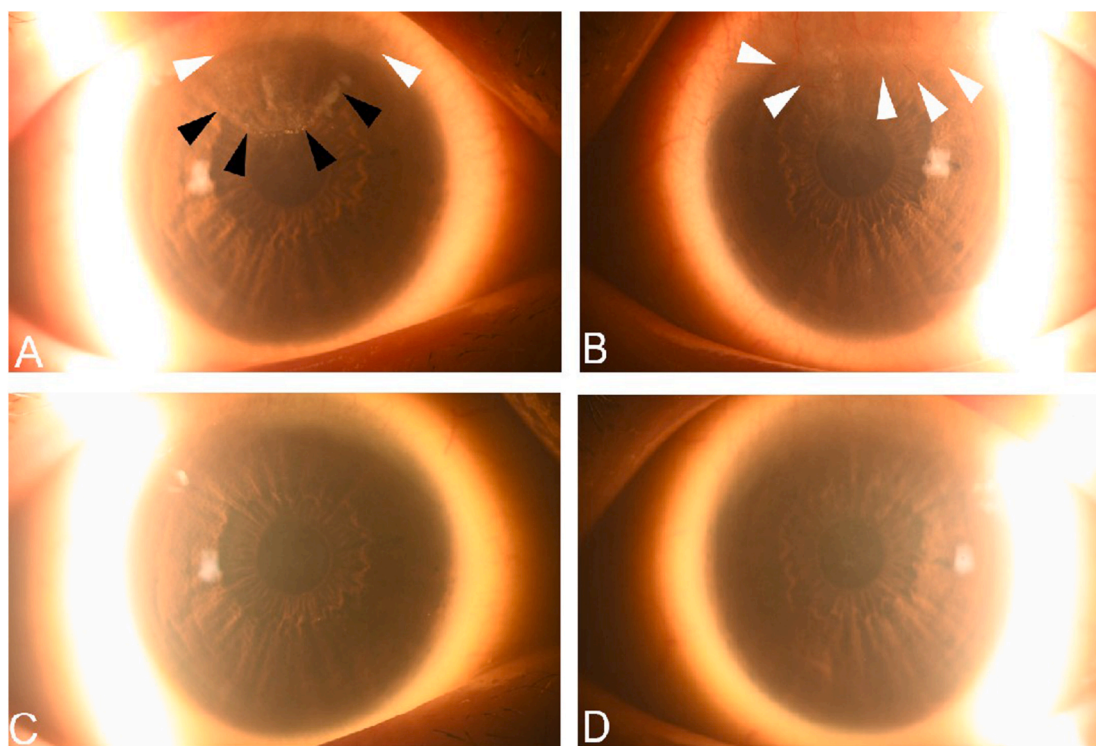


**Fig. 2.** A-C, slit-lamp photograph of the period of exacerbation (December 2020). Corneal neovascularization (black arrowhead) and subepithelial infiltration (white arrowhead) are shown on the patient's right eye (A) and left eye (B). Irregular epithelial surface is also clearly shown on fluorescein staining (C).

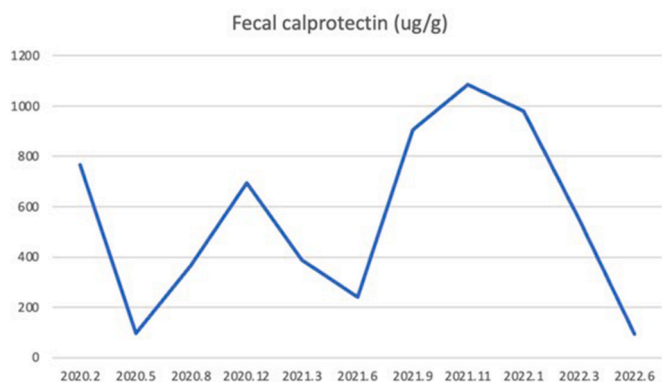
fecal calprotectin levels and found that keratopathy worsened when fecal calprotectin levels increased (Fig. 4). For this finding, tacrolimus 0.1 % twice a day was added. The corneal appearance improved again as fecal calprotectin decreased (Fig. 3C and D), and we plan to follow up after discontinuation of tacrolimus 0.1 % eye drops.

### 3. Discussion

Cases in which Crohn's disease causes keratopathy have rarely been reported, and the exact pathophysiology of Crohn's disease-associated keratopathy is unknown. In this case, the keratopathy findings had a course associated with Crohn's disease activity.



**Fig. 3.** A-B, slit-lamp photograph of the period of recurrence (December 2021). Corneal neovascularization (white arrowhead) had increased again in both eyes, especially in the left eye (B), and subepithelial infiltration (black arrowhead) had increased again even to the right eye (A). C-D, slit-lamp photograph of the period of improvement (February 2022). Tacrolimus 0.1 % twice a day have been used, and as fecal calprotectin decreased at that period, the corneal appearance had improved again.



**Fig. 4.** A graph analyzing the trend of fecal calprotectin value. Calprotectin is abundant in polymorphonuclear neutrophil leukocytes, monocytes, and macrophages. Fecal calprotectin is directly related to the intensity of inflammatory response of intestinal mucosa. It can be used as an indicator for the diagnosis of colon inflammation, including Crohn's disease. It was shown that the patient's keratopathy worsened when fecal calprotectin increased, especially in December 2020 and November 2021.

Due to the characteristics of Crohn's disease, which manifests as an autoimmune mechanism, Crohn's disease-associated keratopathy is also thought to be related to autoimmunity. In this case, the activity of Crohn's was thought to have affected the keratopathy, in which subepithelial infiltration and corneal neovascularization were present. These findings were also reported in other case reports of Crohn's disease-associated keratopathy.<sup>4,5</sup>

Furthermore, for patients with Crohn's disease, attention should be given to changes in the fecal calprotectin level, which is measured regularly in the gastroenterology department. Calprotectin, a member of

the S-100 protein family, is a calcium- and zinc-binding protein predominantly located in neutrophils and distributed throughout the human body. The detection of calprotectin in feces is attributed to the migration of neutrophils into gastrointestinal tissues during inflammatory processes. Elevated fecal calprotectin levels have been positively correlated with intestinal inflammation, making it a useful biomarker for gastrointestinal disorders including Crohn's disease.<sup>7</sup>

Due to the trend of fecal calprotectin levels, this study showed that keratopathy worsened when fecal calprotectin increased. Upon confirming the elevated stool calprotectin level, we consulted the gastroenterology department regarding the potential necessity for additional systemic treatment for Crohn's disease. The gastroenterology team noted that although the stool calprotectin level was elevated and there was associated keratopathy, there were no signs of worsening in endoscopic findings or gastrointestinal symptoms compared to the previous follow-up. Consequently, they recommended maintaining the current systemic and ophthalmic treatment while reducing the follow-up interval. Subsequently, with the reduction in fecal calprotectin level and the continuation of ophthalmic treatment, the keratopathy improved. Treatment of Crohn's disease-associated keratopathy has been reported to involve symptomatic control.<sup>4,5</sup> In other cases keratopathy improved after administering topical steroids, and using artificial tears also helped relieve symptoms, such as foreign body sensations.<sup>4,5</sup> However, in this case, the course of keratopathy was more affected by Crohn's disease activity than by topical eye drops. Topical steroids or autologous serum eye drops did not effectively control keratopathy. Therefore, relieving Crohn's disease activity could be an alternative treatment for Crohn's disease-associated keratopathy. Moreover, to stabilize the course of keratopathy, topical tacrolimus, which has fewer side effects than topical steroids, can be considered for maintenance therapy.

Certain differential diagnoses should be distinguished from the current case, in particular adalimumab-related keratopathy. In addition to Crohn's disease-associated keratopathy, rare cases of keratopathy due to



the side effects of medications used to treat Crohn's disease have been reported. In a case reported in 2014, a patient who received anti-TNF- $\alpha$  therapy for the treatment of Crohn's disease had developed rosacea-like keratopathy with peripheral corneal neovascularization.<sup>8</sup> Other keratopathy cases have been reported as a side effect of adalimumab.<sup>9</sup> However, in this case, the patient's adalimumab dose was constant over time; hence, Crohn's disease-associated keratopathy seemed more likely.

Peripheral ulcerative keratitis (PUK) should also be excluded due to its association with various autoimmune diseases, including rheumatic disease and IBD. However, the characteristic features of PUK, such as corneal thinning and corneal epithelial defect, were absent in this case.

Crohn's disease-associated keratopathy should be suspected in patients with Crohn's disease who had no previous ophthalmologic history and have findings, such as subepithelial infiltration, irregular epithelial surface, and corneal neovascularization that do not improve with persistent use of eye drops. As a treatment, topical steroids and immunosuppressants may be helpful, and managing Crohn's disease activity by referral to the gastroenterology department should be considered. Even if there is a temporary improvement, Keratopathy may recur in accordance with Crohn's disease activity; therefore, continuous ophthalmic follow-up observation is required, considering topical tacrolimus as long-term maintenance therapy. Further research is needed to elucidate the role of Calprotectin and other inflammatory biomarkers in the direct or indirect development of corneal pathology in IBD. After conducting a literature review using the keywords Crohn's disease and keratopathy, we did not find any prior reports of Crohn's disease-associated keratopathy in South Korea.

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## Authorship

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

## Patient consent

Consent to publish this case report has been obtained from the

patient in writing.

## CRediT authorship contribution statement

**Ji Ho Kim:** Writing – original draft. **Yeo Kyoung Won:** Writing – review & editing, Supervision. **Tae-young Chung:** Conceptualization. **Dong Hui Lim:** Writing – review & editing, Supervision.

## 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. There are no financial interests/personal relationships for this article.

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