

Corneal Adverse Events Temporally Associated with Anti-TNF- α Therapy: Severe Fibrovascular Pannus and a Non-Pannus Epitheliopathy in Two Cases

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Purpose: To describe two corneal adverse events temporally associated with anti-tumor necrosis factor- α (TNF- α) therapy—one with severe fibrovascular pannus and another with epithelial keratopathy without pannus.

Methods: Two patients on anti-TNF- α agents underwent comprehensive ocular examinations. Management included modification or discontinuation of biologics as clinically indicated and intensified topical therapy.

Results: Case 1 (pustular psoriasis on adalimumab) developed bilateral fibrovascular pannus with stromal changes. Ocular findings did not improve immediately after adalimumab discontinuation but gradually improved following macrolide, topical corticosteroid, and immunomodulatory therapy. Case 2 (Crohn's disease on adalimumab then golimumab) presented with superior corneal haze and diffuse superficial punctate keratopathy without pannus and resolved with topical therapy alone.

Conclusion: These cases raise the possibility that corneal adverse events—including severe pannus—may occur during anti-TNF- α therapy. Given the heterogeneity and potential confounders, causality cannot be established. Ophthalmic vigilance and further studies are warranted.

Keywords: anti-TNF- α agents, corneal pannus, epitheliopathy, biologic therapy, ocular complications

Introduction

Tumor necrosis factor- α inhibitors (anti-TNF- α) have revolutionized the management of various autoimmune diseases, such as rheumatoid arthritis and inflammatory bowel disease. TNF- α is a key cytokine in inflammatory pathways, playing a pivotal role in leukocyte recruitment and immune regulation.¹ With the expanding use of these biologic therapies, however, reports of ocular adverse effects are emerging.² Paradoxical ocular inflammation, including uveitis and scleritis, has been observed in patients receiving anti-TNF- α .^{3,4} Notably, the soluble TNF receptor etanercept has been specifically linked to new-onset uveitis and scleritis despite otherwise well-controlled systemic disease.^{3,4}

While anti-TNF- α agents are widely used, corneal involvement remains rare, and any association should be considered hypothetical given limited mechanistic and epidemiologic data. Only isolated cases of keratopathy have been documented; for instance, Fasci-Spurio et al reported a sight-threatening rosacea-like keratopathy in a Crohn's disease patient on anti-TNF- α treatment.⁵ Corneal pannus, characterized by the ingrowth of fibrovascular tissue onto the cornea often driven by chronic inflammation and neovascularization,⁶ represents a significant but even less frequently reported corneal complication in this context.

Herein, we report two heterogeneous corneal presentations temporally associated with anti-TNF- α therapy and discuss alternative explanations and limitations.

Methods

Comprehensive ocular examinations were performed, including slit-lamp biomicroscopy and, when indicated, anterior segment optical coherence tomography (AS-OCT). Management strategies were individualized and could include modification or discontinuation of biologic agents alongside intensified topical therapy (eg, corticosteroids, macrolides, immunomodulators) and supportive lubrication.

Ethics: This study adhered to the Declaration of Helsinki and the ARVO statement on human subjects. The protocol—including publication of anonymized case details—was approved by the Medical Ethics Committee of Kanazawa University (Approval No. 114197). Written informed consent for publication, including clinical images, was obtained from both patients.

Work-up limitations: In Case 1, confirmatory testing for tuberculosis (eg, interferon- γ release assay: IGRA) and microbiologic evaluation for *Cutibacterium* (*Propionibacterium*) *acnes* were not performed. In Case 2, Schirmer I testing and fluorescein tear break-up time (fTBUT) were not obtained at presentation. Therapeutic drug monitoring (adalimumab level/anti-drug antibodies) was not performed in either case.

Case Reports

Case 1

A 19-year-old male with pustular psoriasis initiated subcutaneous adalimumab (40 mg biweekly) in November 2019, which was reduced to monthly dosing in May 2020 because of fever. From mid-May 2020, he developed gradual visual loss, ocular pain, and low-grade fever. In August, a local ophthalmologist noted bilateral corneal pannus extending centrally and started topical 0.5% levofloxacin and 0.1% betamethasone four times daily; he was referred to our clinic on August 5.

At presentation, best-corrected visual acuity (BCVA) was 20/2000 in the right eye (OD) and 20/40 in the left eye (OS); intraocular pressures (IOPs) were 11.2 mmHg in both eyes. Slit-lamp examination revealed bilateral blepharitis, conjunctival hyperemia, corneal haze, and neovascularization (Figure 1A and B). AS-OCT showed corneal thinning, focal thickening, and hyperreflective stromal lesions (Figure 1C and D).

Adalimumab was discontinued; however, ocular findings remained unchanged immediately thereafter. Oral clarithromycin (400 mg daily) was initiated, and topical corticosteroids were intensified. Subsequently, topical azithromycin 1% and topical tacrolimus were added. Conjunctival inflammation and blepharitis resolved, and pannus regressed (Figure 1E and F). Final BCVA improved to 20/50 OD and 20/200 OS.

Ocular findings remained unchanged immediately after adalimumab discontinuation; improvement occurred following initiation of oral clarithromycin (400 mg daily) and intensified topical corticosteroid/immunomodulatory therapy.

Case 2

A 21-year-old female with Crohn's disease had received adalimumab since 2017, later switched to golimumab in 2018. She noted progressive visual decline from May 2020. In July, punctate keratitis was diagnosed in the left eye and 0.1% sodium hyaluronate was prescribed. She presented to our hospital on September 26 with suspected corneal degeneration.

On October 7, BCVA was 20/32 in both eyes; IOPs were 17.1 mmHg OD and 16.5 mmHg OS. Slit-lamp examination showed bilateral conjunctival hyperemia and superior corneal haze with diffuse superficial punctate keratopathy (SPK) predominantly superiorly, without corneal neovascularization or fibrovascular ingrowth (ie, no pannus) (Figure 2A–D).

Therapy included therapeutic soft contact lenses, topical 0.5% levofloxacin twice daily, 0.02% fluorometholone twice daily, and 0.1% sodium hyaluronate four times daily. After two weeks, conjunctival injection and SPK improved, allowing discontinuation of the bandage lenses and antibiotics. At six weeks, clinical findings had fully resolved and BCVA improved to 20/16 in both eyes (Figure 2E–H).

Discussion

These cases raise the possibility of corneal adverse events occurring during anti-TNF- α therapy; however, causality cannot be inferred from temporal association alone. Paradoxical ocular inflammation is recognized with anti-TNF- α , yet corneal involvement appears rare.^{3–6}

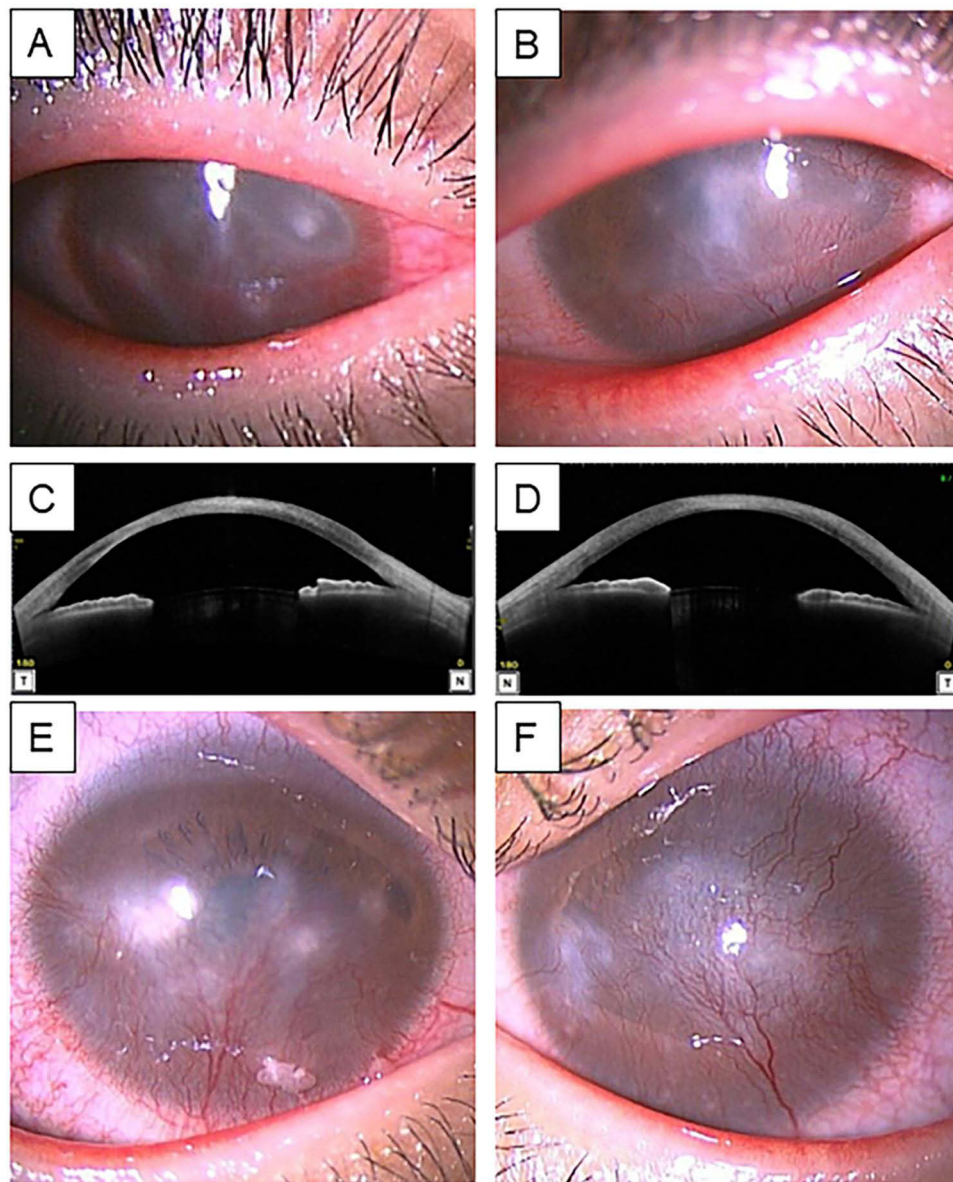


Figure 1 Slit-lamp photographs and anterior segment optical coherence tomography (AS-OCT) images of Case 1. **(A)** Right eye before treatment: Dense fibrovascular pannus was observed. **(B)** Left eye before treatment: Extensive pannus was observed. **(C)** AS-OCT image of the right eye before treatment. Subepithelial hyperreflectivity was noted. **(D)** AS-OCT of the left eye before treatment. Anterior stromal thickening was observed. **(E)** Right eye after 6 weeks of treatment: Regression of pannus and reduced stromal hyperreflectivity. **(F)** Left eye after 6 weeks of treatment: Improvement with residual stromal scarring.

The two presentations likely represent distinct phenotypes: a fibrovascular pannus with stromal involvement (Case 1) versus a non-pannus epitheliopathy with superior haze (Case 2). This heterogeneity suggests potentially different mechanisms and may inform tailored management strategies. Underlying autoimmune disease (pustular psoriasis or Crohn's disease) can manifest with ocular surface disease independently of biologic therapy. Meibomian gland disease-related inflammation and phlyctenular keratitis—including delayed hypersensitivity potentially related to *Cutibacterium* (*Propionibacterium*) *acnes*—are plausible contributors in Case 1.⁷ An infection-related hypersensitivity (eg, tuberculosis) cannot be excluded; adalimumab is associated with increased risk of TB reactivation.^{8,9} Kim et al reported a Crohn's-associated keratopathy; in such reports, concomitant anti-TNF- α therapy represents a potential confounder that cannot be excluded, rather than evidence of adalimumab-induced pannus per se.¹⁰

In Case 1, ocular findings did not improve immediately after discontinuation of adalimumab; improvement followed macrolide, intensified topical corticosteroid, and immunomodulatory therapy. In Case 2, resolution occurred with topical

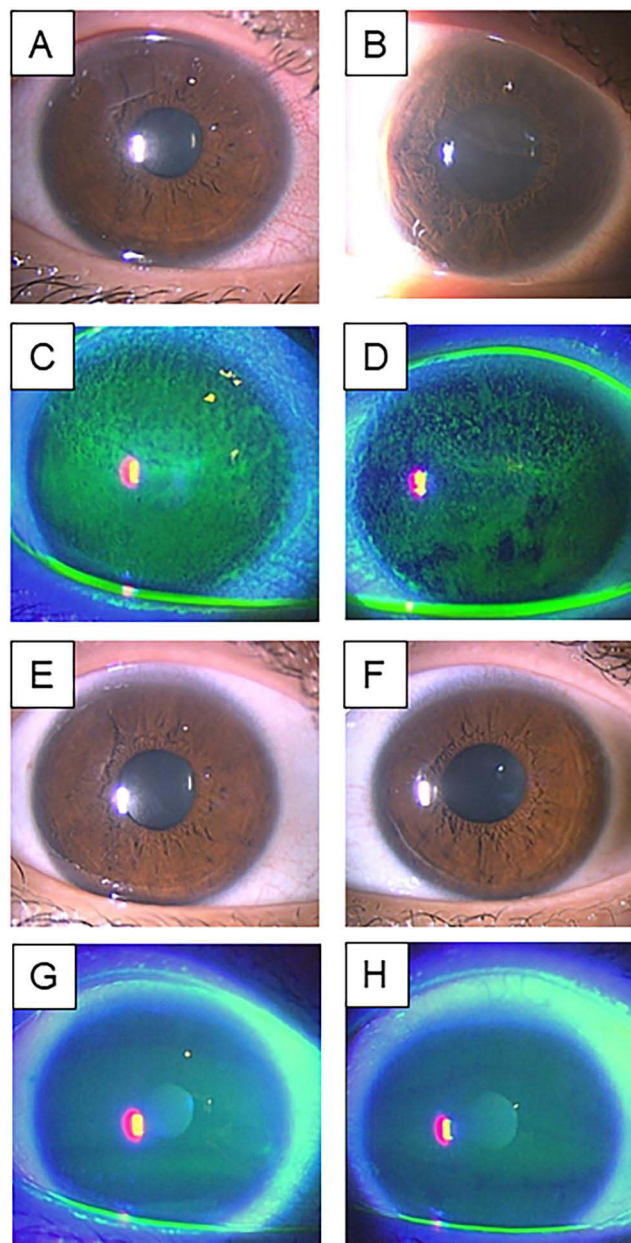


Figure 2 Slit-lamp photographs and fluorescein staining images of Case 2 (non-pannus epitheliopathy). (**A** and **B**) Before treatment: Superior corneal haze with diffuse superficial punctate keratopathy; no fibrovascular ingrowth (pannus) is evident. (**C** and **D**) Fluorescein staining before treatment showing diffuse SPK predominantly superiorly. (**E–H**) After treatment: Resolution of haze and SPK with restored corneal clarity.

therapy alone. These timelines temper any inference that biologic withdrawal was solely responsible for improvement and support a multifactorial process.

Differences in the specific anti-TNF- α (adalimumab in Case 1; golimumab primarily during symptom onset in Case 2 after switching from adalimumab) might also contribute to the varied phenotypes. However, direct comparative data on these events between the two drugs are limited. Studies on anti-TNF- α generally highlight issues such as paradoxical uveitis, other ocular inflammations,¹¹ and corneal problems. Given the lack of robust comparative evidence for adalimumab versus golimumab specifically, vigilant ophthalmic monitoring and further comparative studies are essential for patients receiving these biologics.

Therapeutic drug monitoring (adalimumab levels and anti-drug antibodies) was not performed but may help investigate mechanisms in future cases. Prospective data are needed to define incidence, risk factors, and pathophysiology of corneal events during anti-TNF- α therapy.

Limitations include the absence of IGRA/microbiologic testing in Case 1, lack of tear function tests at presentation in Case 2, no therapeutic drug monitoring (anti-adalimumab quantification to assess serum levels and anti-drug antibodies), and the absence of post-treatment AS-OCT imaging. These limit causal inference; therefore, our observations are hypothesis-generating.

In conclusion, clinicians should maintain vigilance for ocular symptoms in patients receiving anti-TNF- α agents. Early ophthalmic assessment and individualized management are recommended, recognizing heterogeneity and potential confounders. Further studies are warranted.

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References

1. Monaco C, Nanchahal J, Taylor P, Feldmann M. Anti-TNF therapy: past, present and future. *Int Immunol*. 2015;27(1):55–62. doi:10.1093/intimm/idx102
2. Levy-Clarke G, Jabs DA, Read RW, et al. Expert panel recommendations for the use of anti-tumor necrosis factor biologic agents in patients with ocular inflammatory disorders. *Ophthalmology*. 2014;121(3):785–796.e2. doi:10.1016/j.ophtha.2013.09.048
3. Lim LL, Fraunfelder FW, Rosenbaum JT. Do tumor necrosis factor inhibitors cause uveitis? A registry-based study. *Arthritis Rheum*. 2007;56(10):3248–3252. doi:10.1002/art.22918
4. Gaujoux-Viala C, Giampietro C, Gaujoux T, et al. Scleritis: a paradoxical effect of etanercept? Etanercept-associated inflammatory eye disease. *J Rheumatol*. 2012;39(2):233–239. doi:10.3899/jrheum.110865
5. Fasci-Spurio F, Thompson A, Madill S, et al. Sight-threatening keratopathy complicating anti-TNF- α therapy in Crohn's disease: a case report. *Inflamm Bowel Dis*. 2014;20(1):E2–E3. doi:10.1097/01.MIB.0000436952.88522.77
6. Chang JH, Gabison EE, Kato T, Azar DT. Corneal neovascularization. *Curr Opin Ophthalmol*. 2001;12(4):242–249. doi:10.1097/00055735-200108000-00002
7. Suzuki T. Meibomian glands and ocular surface inflammation. *Cornea*. 2012;31(Suppl 1):S6–S10.
8. Venkatesh P, Garg S, Vohra R, et al. Phlyctenular keratoconjunctivitis in children: clinical features and association with tuberculosis. *Indian J Ophthalmol*. 2008;56(2):103–106. doi:10.4103/0301-4738.39113
9. Dixon WG, Hyrich KL, Watson KD, et al. Drug-specific risk of tuberculosis in patients with rheumatoid arthritis treated with anti-TNF therapy: results from the British society for rheumatology biologics register (BSRBR). *Ann Rheum Dis*. 2010;69(3):522–528. doi:10.1136/ard.2009.118935
10. Kim JH, Won YK, Chung TY, Lim DH. Crohn's disease-associated keratopathy: a case report. *Am J Ophthalmol Case Rep*. 2024;36:102186. doi:10.1016/j.ajoc.2024.102186
11. Lim LL, Fraunfelder FW, Suhler EB, et al. Ocular adverse events associated with Adalimumab, infliximab, and etanercept: a retrospective cohort study. *Ophthalmology*. 2012;119(9):1917–1922. doi:10.1016/j.ophtha.2012.03.020

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