

Case report

Concomitant herpes simplex keratitis and autoimmune-associated ulcerative keratitis in rheumatoid arthritis patients

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ARTICLE INFO

Keywords:

Herpes simplex keratitis
 Autoimmune-associated ulcerative keratitis
 Rheumatoid arthritis
 Immunosuppressive therapy
 Biological agents

ABSTRACT

Purpose: To describe four cases of concomitant herpes simplex keratitis (HSK) and autoimmune-associated ulcerative keratitis (UK) in patients with rheumatoid arthritis (RA).

Observations: All patients developed HSK and UK while undergoing treatment for RA. The average age of onset for RA, UK and HSK was 49.3, 69.5 and 70.5 years, respectively. UK preceded HSK in three cases and followed HSK in one case. Two patients had bilateral UK and two had unilateral UK. HSK was unilateral in all cases. All the cases had been treated with immunosuppressive agents including steroid, methotrexate, calcineurin inhibitors, etanercept and tocilizumab at the onset of HSK. Every patient was treated for HSK with topical acyclovir ointment combined with oral valacyclovir. The final visual outcome was extremely poor despite intensive therapy.

Conclusions and Importance: These cases raise the possibility that RA patients have an increased risk of HSK, and that HSK may tend to be severe in these patients because of their immunocompromised condition. Furthermore, the complication of HSK and UK in RA patients is difficult to treat because of the atypical clinical manifestation. Thus, the emergence of corneal ulcer, especially in patients with a long clinical history of RA, calls for careful follow-up.

1. Introduction

Rheumatoid arthritis (RA) can cause a variety of ocular manifestations. Among them, autoimmune-associated ulcerative keratitis (UK) is the most severe, calling for prompt diagnosis and management.¹ Although autoimmune-associated UK usually occurs in the peripheral area of the cornea and is commonly known as “peripheral ulcerative keratitis”, it can also occur, less commonly, in the central area. Thus, this report uses the simpler term “UK” to refer to this condition. By contrast, herpes simplex keratitis (HSK) is caused by a virus, herpes simplex virus-1 (HSV-1). It is one of the most common causes of corneal opacification and infection-related visual morbidity.² Furthermore, accurate diagnosis can be difficult due to atypical manifestations, although the typical manifestation in epithelial HSK is dendritic and geographic ulcers.³ Accurate diagnosis is especially important for

patients with RA or other autoimmune diseases, because UK sometimes becomes complicated with these conditions and has to be treated with steroid or other immunosuppressive agents, which can worsen epithelial HSK.⁴ Complication with UK in particular can exacerbate the condition of patients with HSK. HSK is treated with antiviral medication, while UK is treated with steroid or other immunosuppressive agents, and thus, when a patient's condition worsens, it is hard to judge whether HSK or UK is the cause. Moreover, decreasing immunosuppressive therapy for the treatment of epithelial HSK can lead to the aggravation of UK or RA. This can greatly complicate treatment strategies. While the prevalence of UK in RA patients has been reported to be ~3%, it seems to be less than in the past, possibly due to an improvement in RA in many patients who take non-biological disease-modifying antirheumatic drugs (DMARDs) or biological anti-tumor necrosis factor (TNF)- α inhibitors.^{5,6} However, these are immunosuppressive therapies and

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<https://doi.org/10.1016/j.ajoc.2020.100648>

Received 13 February 2019; Received in revised form 17 February 2020; Accepted 3 March 2020

Available online 09 March 2020

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Abbreviations

HSK	herpes simplex keratitis
UK	ulcerative keratitis
RA	rheumatoid arthritis
DMARDs	non-biologic disease-modifying antirheumatic drugs
TNF	tumor necrosis factor
PCR	polymerase chain reaction
PSL	prednisolone

BMZ	betamethasone
MTX	methotrexate
CsA	cyclosporine A
Tac	tacrolimus
ETN	etanercept
TCZ	tocilizumab
LT	limbal transplantation
PKP	penetrating keratoplasty

may increase the risk of both viral infections and their reactivation. Some previous reports have shown that an increased risk of herpes zoster in RA patients is associated with the use of non-biological DMARDs or biological agents such as TNF- α inhibitors.⁷⁻¹⁰ Although the incidence rate of HSK in RA patients and the effect of immunosuppressive therapy for RA on the risk of HSV infections, including HSK, are not well known, Larrañaga Fragoso et al. recently described five patients who developed HSK under immunosuppressive therapy for RA, and reported that their characteristics differed from immunocompetent patients with HSK.¹¹ Epithelial HSK in RA patients is often multiple, geographic, and covers a large area of the cornea, limbus and the conjunctival epithelium. Moreover, cases with stromal HSK are more aggressive and difficult to manage, with a high incidence of gram-positive superinfections and corneal perforation. However, reports on HSK in RA, especially when it is complicated with UK, are still few. Nevertheless, this condition is very challenging and calls for careful management. Here, we report four cases of concomitant HSK and UK in RA patients. We describe the clinical characteristics of these cases, and hope that this will lead to improved HSK and UK management in RA patients. This study was approved by the Institutional Review Board of Tohoku University Hospital and was conducted in accordance with the tenets of the Declaration of Helsinki (2017-1-553).

2. Findings

Among 821 patients with RA examined at the rheumatology outpatient clinic of Tohoku University Hospital between April 2003 and October 2018, HSK and UK were diagnosed in 6 patients (0.7%) and 12 patients (1.4%), respectively. Concomitant HSK and UK was diagnosed in 4 patients (0.5%). A clinical summary of the four cases is shown in Table 1. Slit-lamp photographs of the anterior segment for each case are shown in Figs. 1 and 2. The diagnosis of HSK was based on the presence of dendritic or geographic ulcers evaluated by at least two corneal specialists. In some cases, polymerase chain reaction (PCR) examination of corneal scrapings or tears was also adjunctively performed. The diagnosis of UK was based on the typical manifestation of peripheral corneal ulcer. However, cases with corneal ulcer not in the peripheral area were also diagnosed as UK when there were no dendritic or geographic ulcers, or PCR examination did not reveal the presence of HSV-1. One patient was male and 3 patients were female. The average age at the onset of RA, UK and HSK was 49.3, 69.5 and 70.5 years, respectively. The average duration between the onset of RA and the onset of UK and HSK was 20.3 and 21.3 years, respectively. HSK was unilateral in all cases. Two patients had bilateral UK (cases 1 and 2) and 2 patients had unilateral UK (cases 3 and 4). Unilateral UK occurred in the same eye as HSK in case 4 and in the opposite eye in case 3. All 4 patients were undergoing treatment for RA at the onset of HSK. UK preceded HSK in 3 cases and UK followed HSK in 1 case. Systemic immunosuppressive treatments at the onset of HSK were as follows: steroid in every patient (prednisolone [PSL] 25 mg/day in case 1, betamethasone [BMZ] 1 mg/day in case 2 and 3, and PSL 5 mg/day in case 4), methotrexate (MTX) in 3 patients (cases 1, 2 and 4), calcineurin

inhibitors (cyclosporine A; CsA and tacrolimus; Tac) in 3 patients (CsA in cases 1 and 2, and Tac in case 4), etanercept (ETN) in 1 patient (case 1) and tocilizumab (TCZ) in 1 patient (case 3). Three patients were being treated with topical immunosuppressive agents at the onset of HSK, as follows: BMZ in 3 patients (cases 1, 2 and 4) and CsA in 2 patients (cases 1 and 2). Serological findings are shown in Table 2. Although we could not obtain a definite diagnosis of Sjögren's syndrome (SS) in the current case series because detailed examinations and biopsies were not performed in each case, case 1 was positive for SS-A antibodies. All cases were negative for anti-neutrophil cytoplasmic antibodies (ANCA).

Case 1 was a 62-year-old male. ETN was started after the onset of UK to control disease activity. Corneal ulceration progressed despite increasing the immunosuppressive treatment with oral PSL to 30 mg/day and administering CsA both topically and systemically. Thus, we performed limbal transplantation (LT) in the eye. HSK occurred 1 month postoperatively.

Case 2 was a 64-year-old female. Corneal perforation due to UK suddenly occurred in the central area of the cornea in both eyes during treatment for RA with MTX at 8 mg/week. Although UK in the central area is unusual in RA patients, we considered that this corneal perforation was caused by autoimmune-associated UK because it was bilateral and without dendritic or geographic ulcers. Penetrating keratoplasty (PKP) was performed in both eyes sequentially. HSK occurred in the left eye 2 months postoperatively, during additive postoperative immunosuppressive treatment with BMZ and CsA, administered both systemically and topically.

Case 3 was an 85-year-old female. UK developed in the right eye during treatment for RA with TCZ and Tac. The UK was treated with additive topical 0.1% fluorometholone eye drops and oral BMZ at 1 mg/day. Two years later, a corneal ulceration in the paracentral area developed in the fellow eye. At first, autoimmune-associated UK was suspected because of the clinical history of the right eye, and BMZ eye drops were added. However, the corneal ulceration progressed to a geographic ulcer, followed by corneal perforation. PCR examination of corneal scrapings revealed the presence of HSV-1. Although we considered that the corneal ulceration was originally caused by HSK, it is possible that UK in fact preceded HSK in this eye.

Case 4 was a 67-year-old female. In this case, we consider that UK occurred after HSK. The patient had a past history of bilateral scleritis resulting in chorioretinal atrophy in both eyes after the onset of RA. Thus, BMZ eye drops had been prescribed, until a geographic ulcer with corneal perforation emerged during treatment for RA (MTX at 12 mg/week and PSL at 5 mg/day). PCR examination of tear samples revealed the presence of HSV-1. Although corneal epithelization was initially achieved with antiviral treatment, corneal perforation re-occurred without the typical manifestations of HSK (i.e., dendritic or geographic ulcer) a few weeks later. A PCR examination of new tear samples was performed, with results negative for HSV-1. Although PCR testing of corneal scrapings has higher sensitivity,¹² tear samples were used because obtaining them is less invasive in patients with corneal perforation. Culture testing of corneal scrapings was also negative. Thus,

Table 1
Clinical summary.

Case	Sex	Age at the onset of	Duration from RA onset		Laterality of UK/ HSK		Region of UK/ HSK	Immunosuppressive treatment at the onset of HSK		Surgical intervention for UK	Perforation	PCR	Treatment for HSK	VA at the onset of HSK	Final VA
			To UK	To HSK	HSK	HSK		Systemic	Topical						
1	M	52	62	63	10	11	B/L	P/D	MTX 6mg/day, ETN Csa, PSL 25mg/week, Csa, BMZ	LT	-	N.D	ACV ointment	0.03	0.01
2	F	50	64	65	14	15	B/L	C/C	MTX 2mg/day, Csa, BMZ 1mg/day, Tac, BMZ 1mg/day, TCZ	PKP	+	N.D	ACV ointment	0.02	0.06
3	F	47	85	87	38	40	R/L	P/D	-	-	+	+	ACV ointment, VACV p.o.	CF	HM
4	F	48	67	67	19	19	R/L	P/D	MTX 12mg/week, PSL 5mg/day	BMZ	+	+	ACV ointment, VACV p.o.	HM	NLP

M = male, F = female, RA = rheumatoid arthritis, UK = ulcerative keratitis, HSK = herpes simplex keratitis, B = bilateral, R = right, L = left, P = peripheral, D = diffuse, C = central, MTX = methotrexate, Csa = cyclosporine A, PSL = prednisolone, ETN = etanercept, BMZ = betamethasone, Tac = tacrolimus, TCZ = tocilizumab, LT = limbal transplantation, PKP = penetrating keratoplasty, N.D = no data, ACV = acyclovir, VACV = valacyclovir, p.o. = per os (internally), VA = visual acuity, CF = counting fingers, HM = hand motion, NLP = no light perception.

autoimmune-associated UK and relapsed scleritis was suspected. Immunosuppressive therapy was increased to intravenous methylprednisolone at 500 mg/day for 3 days, followed by oral PSL at 30 mg/day. Despite this intensive therapy, the patient's condition did not improve and progressed to no light perception.

Every patient in this case series was treated for HSK with topical ACV ointment, and cases 3 and 4 also received oral VACV. The basic treatment strategy for our patients was to increase immunosuppressive therapy after the onset of UK and to gradually decrease this therapy in the presence of epithelial HSK, in consultation with rheumatologists. However, the concomitant nature of the HSK and UK made the management of these cases difficult, and the final visual outcome was very poor in each case.

3. Discussion

We found that the prevalence of HSK and UK in the RA patients in this study was 0.7% (6/821) and 1.4% (12/821), respectively, while the prevalence of concomitant HSK and UK was 0.5% (4/821). All these cases were undergoing treatment for RA with common immunosuppressive agents, such as steroids or TNF-α inhibitors, at the onset of HSK. A previous study reported that the incidence rate of HSK was 9.2 per 100,000 per year.¹³ Although the incidence rate of HSK in RA patients and the effect of immunosuppressive therapy for RA on the risk of HSK have not yet been definitively determined, our study showed that concomitant HSK and UK is nevertheless very dangerous, as the visual outcome after treatment was very poor in each case we examined.

The average RA duration at HSK onset in our cases was 21.3 years (range: 11–40 years), which is similar to the average duration of 19.6 years (range: 14–20 years) reported by Larrañaga Frago et al.¹¹ A number of previous reports have indicated that RA might increase the risk of herpes virus infection due to dysregulation of the immune system.^{14–16} Moreover, a high cumulative dose of steroids is associated with an increased risk of infection.¹⁷ This suggests that long-term immunosuppressive treatment for RA might be a risk factor for HSK. At the same time, we consider that increasing immunosuppressive therapy, even over a relatively short span of time, might also increase the risk of infection, as we described in the findings section.

Different biological agents were used in 2 cases at the onset of HSK: ETN in case 1 and TCZ in case 3. ETN is a TNF-α inhibitor and TCZ is an anti-interleukin-6 receptor monoclonal antibody that was developed in Japan to treat RA. Larrañaga Frago et al. also reported 2 cases in which HSK occurred during treatment for RA with either ETN or TCZ.¹¹ Although it is uncertain whether there is a higher risk of HSK during TNF-α inhibitor or TCZ treatment, some previous studies have reported an increased risk of herpes zoster in RA patients, associated with the use of non-biological DMARDs or biological agents including TNF-α inhibitors and TCZ.^{7–10} Moreover, there is a study reporting differences in the incidence rate of herpes zoster and herpes simplex virus infections in RA patients receiving treatment with different biologic drugs. Tofacitinib had a significantly higher incidence rate (7.61/100 person-years) than other biologic drugs, including ETN, TCZ, abatacept, adalimumab, certolizumab, golimumab, infliximab and rituximab (incidence rates ranging from 5 to 6/100 person-years).¹⁸ Additionally, in some previous reports, steroid treatment has been shown to increase the risk of HSK in rabbit models.^{4,19} Thus, while there is no clear evidence that TCZ and ETN directly increase the risk of HSK, our findings suggest that there is a possibility that these immunosuppressant agents also increase the occurrence of HSK when combined with steroids or other immunosuppressant agents i.e., MTX and calcineurin inhibitors, such as Csa and Tac, during treatment for RA.

In two cases, HSK occurred after surgical intervention (LT and PKP) for UK. Donor to host transmission of HSV-1 can cause graft failure after keratoplasty.²⁰ However, it is uncertain if the HSV-1 came from the donor corneas or was new in these cases. Our research group recently

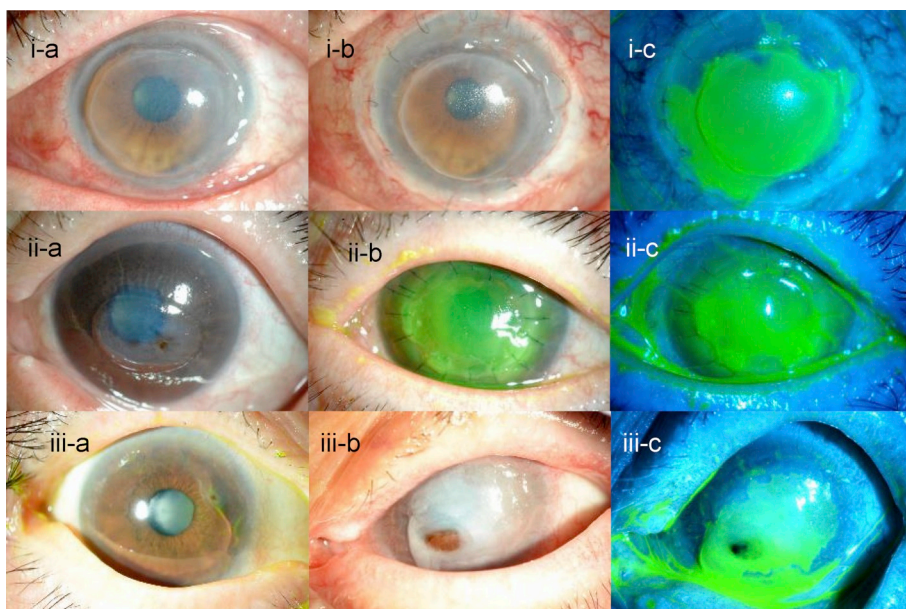


Fig. 1. Slit-lamp photographs of cases 1 (i-a - i-c), 2 (ii-a - ii-c) and 3 (iii-a - iii-c). I-a: Autoimmune-associated ulcerative keratitis (UK) is circumferential in the peripheral area. I-b: Melting of the graft after limbal transplantation is visible. I-c: Fluorescein-stained photograph of the same area as i-b, showing a geographic ulcer indicative of herpes simplex keratitis (HSK). II-a: Autoimmune-associated UK with a corneal perforation visible in the central area. II-b: A corneal ulceration has emerged in the corneal graft after penetrating keratoplasty. II-c: Fluorescein-stained photograph of the same area as ii-b, showing a geographic ulcer indicative of HSK. III-a: Old autoimmune-associated UK is visible in the upper nasal peripheral area in the right eye. III-b: A corneal perforation is present in the paracentral area in the fellow eye. III-c: Fluorescein-stained photograph of the same area as iii-b, showing a geographic ulcer indicative of HSK.

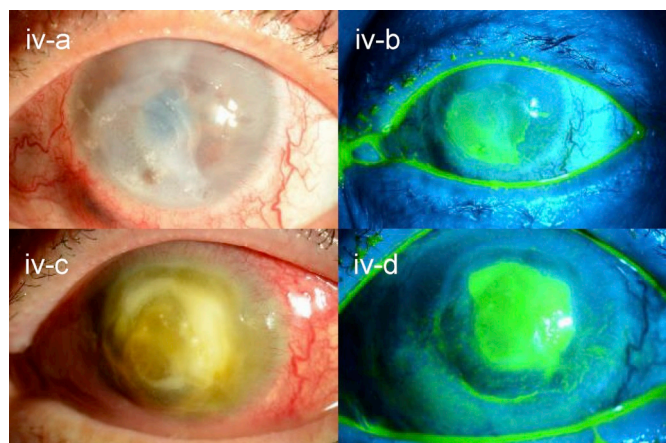


Fig. 2. Slit-lamp photograph of case 4. IV-a: A diffuse corneal ulceration is visible from the central to lower nasal area of the cornea, with perforation. IV-b: Fluorescein-stained photograph of the same area as iv-a, showing a geographic ulcer indicative of HSK. IV-c: Although epithelization was achieved after antiviral treatment, the corneal perforation re-occurred a few weeks later. Scleritis is also visible. IV-d: Fluorescein-stained photograph of the same area as iv-c, showing no geographic ulcer indicative of autoimmune-associated UK.

Table 2
Serological findings.

Case	Sex	RF (IU/ml)	Anti-CCP (U/ml)	Anti-SS-A (U/ml)	Anti-SS-B (U/ml)	ANA (fold)	ANCA (IU/ml)
1	M	55	424.1	113.6	-	80	-
2	F	168.1	59.2	-	-	1280	-
3	F	260.9	84.1	-	-	80	-
4	F	1213.5	86.7	-	-	160	-

M = male, F = female, RF = rheumatoid factor, CCP = cyclic citrullinated peptide, SS = Sjögren's syndrome, ANA = antinuclear antibody, ANCA = anti-neutrophil cytoplasmic antibody, - = negative Blood tests were performed at the onset of autoimmune-associated ulcerative keratitis in cases 1 and 2, and at the onset of herpes simplex keratitis in cases 3 and 4.

reported that multiplex PCR can be used to screen infectious agents in corneal tissue from transplant recipients and donors.²¹ Although we did not perform this type of screening for the cases in the current report because the technique was unavailable at the time, such screening has

the potential to reduce the risk of postoperative infection, not only by HSK but also by bacteria and fungi. However, we did use PCR as a diagnostic tool in some cases in the current report. PCR has the advantages for diagnosing HSK of high sensitivity and a short processing time²² potentially enabling prompt diagnosis and appropriate treatment in these complicated cases. In case 4, PCR examination was helpful to distinguish UK from relapsed HSK. Even after HSK is diagnosed, it is important to differentiate it from the occurrence of autoimmune-associated UK.

4. Conclusions

This report describes four cases of concomitant HSK and autoimmune-associated UK in RA patients. These cases raise the possibility that RA patients have an increased risk of HSK, and that HSK may tend to be severe in these patients because of their immunocompromised condition. Furthermore, we consider that the difficult clinical management of concomitant HSK and UK makes it essential to consult with rheumatologists to optimize the total treatment strategy. Thus, the emergence of corneal ulcers, especially in patients with a long clinical history of RA, calls for careful follow-up.

Patient consent

This study was observational and human body samples were not specially obtained for the research. Therefore, instead of obtaining informed consent, information on the purpose and implementation of the research was released on the website of Tohoku University Graduate School of Medicine.

Funding

No funding or grant support.

Declaration of competing interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

Acknowledgements

The authors thank Mr. Tim Hilts for reviewing this manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ajoc.2020.100648>.

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