Severe Cutaneous Adverse Reactions during Tapering of High-Dose Systemic Steroid Therapy for Autoimmune Diseases: Implications for Non-HIV Immune Reconstitution Inflammatory Syndrome

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Abstract
We present 2 cases of severe cutaneous adverse reactions (SCARs) during the tapering of corticosteroids, following several courses of high-dose pulse therapy for Vogt-Koyanagi-Harada disease. Their general symptoms and mucous membrane lesions, including those of the eye, were milder than those usually seen in Stevens-Johnson syndrome/toxic epidermal necrolysis. Based on their initial presentation, these cases were not initially identified as SCARs, but continued to progress over the course of a few days. The mechanism underlying the paradoxical response to steroid administration seen in these patients can be interpreted as immune reconstitution inflammatory syndrome in human immunodeficiency virus-negative patients.
Introduction

Corticosteroids are used for the treatment of patients with early-stage Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN). However, the administration of high-dose corticosteroids in certain patients with conditions such as collagen disease, autoimmune disorders, or brain tumours may induce SJS/TEN [1, 2]. This is surprising considering that corticosteroids have anti-inflammatory effects and are potent immunosuppressors. Although the mechanisms underlying this paradoxical response remain unknown, systemic corticosteroids are considered a risk factor for the onset of SJS/TEN [2].

Immune reconstitution inflammatory syndrome (IRIS) encompasses a range of conditions, including infectious and immunological diseases that are triggered (or are exacerbated) during immune response recovery following anti-retroviral therapy (ART) for human immunodeficiency virus (HIV) [3]. Similar events have been recognised in non-HIV patients when immunosuppressive agents, including corticosteroids, are abruptly stopped or reduced, resulting in immune reconstitution [4–7].

Herein we present 2 cases of severe cutaneous adverse reactions (SCARs) during the tapering of high-dose systemic steroid therapy for Vogt-Koyanagi-Harada disease. When considered possible non-HIV IRIS, the mechanism underlying the onset of SJS/TEN during steroid administration in these cases can be well understood.

Case Report

Case 1

A 38-year-old man presented with a generalised rash showing mucous membrane involvement and a slight fever. He had developed Vogt-Koyanagi-Harada disease 4 weeks previously and four courses of steroid pulse therapy were administered in our ophthalmology department. A day after the last pulse therapy, we began tapering prednisolone (PSL). Erythematous plaques on the face, trunk, and palms developed after administration of PSL at a dose of 40 mg/day (Fig. 1). Mucous membrane involvement, as shown by lip erosion and conjunctival congestion, was also observed. The body temperature was 37.7°C. Closer examination revealed round, up to fingertip-sized erythematous plaques and confluent erythema on the face, trunk, and limbs; some of the plaques had flaccid bullae and erosions (Fig. 2a, b). Histological analyses indicated extensive necrosis of epidermal cells and cleft formation at the epidermal dermal boundary (Fig. 2d, e). Epidermal detachment was observed over 30% of the body surface area and a diagnosis of TEN was made (Fig. 2c). Comparisons of blood counts performed 6 days before the onset of skin lesions with those performed the day after onset revealed a ~50% increase in white blood cells and an almost 20% increase in lymphocytes. Based on these observations, PSL was increased to 70 mg/day for the treatment of TEN. Eye symptoms, such as mild and pseudomembranous conjunctivitis and corneal erosions, were not observed. We slowly tapered PSL to the maintenance dose for Harada disease (20 mg/day). Neither recurrence nor sequelae were observed. Rebamipide was the only medication other than PSL taken before the onset of TEN. Lymphocyte transformation tests (LTTs) for rebamipide and PSL at 2 months after onset were negative when PSL was maintained at 20 mg/day for Harada disease. Control cpm was low at 92. Hence, it was not possible to identify the antigen for TEN. Antibody titres revealed no evidence of reactivation of EB virus, herpes simplex virus, or cytomegalovirus (CMV), nor was any elevation of anti-mycoplasma
antibodies observed. In this case, the general symptoms and mucous membrane lesions, including those with eye involvement, were milder than is typically seen in TEN.

**Case 2**

A 48-year-old female presented with a 2-day history of erythematous plaques on the trunk. She was suffering from Vogt-Koyanagi-Harada disease and had received three courses of steroid pulse therapy 4 weeks previously (Fig. 3). Famotidine and methylprednisolone were being taken simultaneously, while rabeprazole sodium was started alongside steroid pulse therapy, which then continued with PSL. After a few days, the PSL dose was reduced to 15 mg/day and scattered, erythematous plaques appeared on the trunk. An initial examination revealed reddish, azuki bean-sized papules and erythematous plaques on the trunk (Fig. 3a). The mucous membranes were not affected. The body temperature was 36.4°C. Laboratory examination results were all within the normal range. The culprit drug, rabeprazole sodium, was discontinued while PSL was maintained at 15 mg/day. Clinical findings on admission were not suggestive of SCARs, but erythematous plaques progressed rapidly over the course of 2 days. Physical examination on admission revealed no fever and irregularly shaped, erythematous plaques on the trunk and limbs. Some blisters on erythematous plaques were found on the feet. Mucous membrane involvement was not observed. A skin biopsy was performed under a clinical diagnosis of erythema multiforme. Histologically, vacuolar degeneration of basal cells admixed with individual cell necrosis was observed. A number of lymphocytes had infiltrated into the dermal-epidermal interface (Fig. 3b). The LTT for rabeprazole sodium on admission was positive (stimulation index, SI = 2.3) when PSL was tapering at 15 mg/day. In the control, cpm with no addition was 5,304, and after PHA stimulation, it was 119,638, and PHA-SI was 22.6. However, it was negative (SI = 1.2) 49 days later, when PSL was maintained at 20 mg/day for Vogt-Koyanagi-Harada disease. In the control at this point, cpm with no addition was 11,366, and after PHA stimulation it was 96,415, and PHA-SI was lowered to 8.5. Oral PSL was increased to 70 mg/day for 2 weeks and then slowly tapered to the maintenance dose for Harada disease (20 mg/day). Epidermal detachment peaked at ~6% of the body surface area (Fig. 3c). No evidence of reactivation of EB virus was detected during the course of disease based on antibody titres. Levels of antibodies to mycoplasma were not elevated. Comparisons of blood counts performed before and after the onset of skin lesions revealed no changes in the number of white blood cells; however, the number of lymphocytes decreased by about 50% (3,750–1,680/μL). After onset, CD4+ and CD8+ cells accounted for 40 and 20.9% of lymphocytes, respectively, for a CD4/CD8 ratio of 1.93.

**Discussion**

We herein present 2 cases of SJS/TEN in patients with Vogt-Koyanagi-Harada disease that developed during the tapering of systemic steroids following high-dose pulse therapy. The clinical features of our cases included a lack of high fever and severe eye involvement, and failure to fulfil the diagnostic criteria for SJS/TEN. However, membranous desquamation, which indicates epidermal necrosis during the regression period, prompted us to consider a diagnosis of SJS/TEN. Although we were not able to diagnose case 2 as SJS based on the diagnostic criteria, we believe that the actual disease state of the patients is consistent with SJS/TEN; the mild disease courses are likely due to the masking effects of steroids.

The European Severe Cutaneous Adverse Reactions (EuroSCAR) study (379 patients, 1,505 controls) assessed the risks associated with the medications used to treat SJS/TEN [8].
The study reported that many patients had been exposed to steroid therapy before the onset of SJS/TEN (14.8% compared to 2.1% of controls), but in 55% of such cases another highly suspected medication was also involved. The study could not conclude definitively whether corticosteroids are a direct cause of SJS/TEN, or a risk factor that modifies the immune response [8].

The reason for considering the presented case as an event of IRIS is as follows. We note that SJS/TEN did not occur during high-dose steroid use in the present cases, nor in previously reported cases, but has been reported during the tapering or maintenance dose periods. Draft diagnostic criteria for non-HIV IRIS have been proposed, with the condition broadly defined as inflammatory events that occur in various organs in response to antigens, including medications and pathogenic microorganisms, which are assumed to have existed prior to recovery from the impaired immune state. These inflammatory events manifest within a few months and/or are exacerbations of inflammatory events that had already occurred (or were treated) before immune reconstitution [9]. Present cases met the inclusion and exclusion diagnostic criteria. In case 1, pre-existing antigen-specific antibodies were not identified prior to the onset of TEN because rebamipide was the only medication used before immune recovery; an LTT for rebamipide was negative and no cases of SJS/TEN caused by rebamipide have previously been reported. In case 2, the culprit drug was rabeprazole sodium ingested since steroid pulse therapy; an LTT for this agent was positive on admission, but it turned negative 49 days later. In the control of this case, cpm with no addition and after PHA stimulation were rather high. This is because lymphocytes would proliferate without stimulation by causative drug during immune recovery. Hence, it was not possible to identify the causative antigen certainly in our cases.

Steroid pulse therapy is usually applied to treat the acute symptoms of Harada disease [10]. In both of our cases, multiple courses of pulse therapy using methylprednisolone had been administered approximately 4 weeks prior to the onset of SJS/TEN. Increased lymphocyte counts at the onset of TEN in case 1 could suggest immune recovery from high-dose steroid therapy, whereas the relative percentage of lymphocytes was decreased at the onset of skin lesions in case 2. In some IRIS events with severe inflammatory symptoms, neutrophils may dominate the acute phase. A previous study found that the expression levels of CD4+CD25high cells and plasma interleukin-10, as well as the Foxp3/CD3 ratio, were increased 48 h after pulse therapy with methylprednisolone (1 g/day for 3 days) in patients with multiple sclerosis; however, all of these markers of immunosuppression returned to baseline values 6 weeks after treatment [11]. These changes in regulatory T cells (Tregs) and related cytokines suggest that recovery from immunosuppression occurs several weeks after steroid pulse therapy [11]. Abrupt reduction or discontinuation of steroids and immunosuppressive agents other than steroid pulse therapy temporarily reduces the function of Tregs. We previously reported the development of idiopathic thrombocytopenic purpura at the end of pregnancy in a post-partum patient, followed by the development of TEN 4 weeks later during the tapering of PSL from 45 to 20 mg/day without high-dose pulse therapy [12]. The number of Tregs increases during early pregnancy to protect the foetus, peaking during the second trimester, and decreasing thereafter from late pregnancy to after birth [13]. Underlying conditions, such as collagen and autoimmune diseases not limited to Vogt-Koyanagi-Harada disease, have also been proposed as risk factors for SJS/TEN [14, 15].

The possibility of non-HIV IRIS could partly explain the onset of SJS/TEN during steroid administration. It is important in patient management to consider the concept of IRIS because if a steroid is believed to be the causative agent, or if a steroid reactivates the virus to induce SJS/TEN and is then abruptly reduced or discontinued, IRIS will progress and SJS/TEN will be
further exacerbated. When a skin lesion in an SJS/TEN patient is considered to indicate IRIS, the standard approach is to increase the dose of corticosteroid. In our cases, the process of immune recovery was not sufficiently examined. It is necessary to examine sequential changes in the effector T cell/Treg ratio and related cytokines that could act as biomarkers of immune recovery. In the presented cases, viral reactivation or infection (e.g., CMV) could not be confirmed, but it is necessary to diagnose IRIS accurately. Additional cases should be recorded, including detailed virus detection.

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Statement of Ethics

All subjects provided written informed consent to publish their case (including images).

Disclosure Statement

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Author Contributions

All authors contributed significantly to, and all authors are in agreement with, the content of this paper. Dr. Watanabe was the responsible doctor for case 1, and Dr. Kitami was the responsible doctor for case 2. Dr. Sueki prepared the main text, and Dr. Watanabe prepared the figures.

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Fig. 1. Onset and course of case 1. The photograph shows the fundus findings of case 1. Toxic epidermal necrolysis developed 4 weeks after four courses of steroid pulse therapy for Vogt-Koyanagi-Harada disease.
Fig. 2. Clinical and histological findings of case 1. 

a Erythematous plaques on the face associated with mucous membrane involvement, reflected in lip erosion and conjunctival congestion. 

b Confluent erythema with flaccid bullae and erosions on the trunk. 

c Areas of epidermal detachment manifested with membranous desquamation in the regression period. 

d, e Extensive necrosis of epidermal cells and cleft formation at the epidermal dermal boundary shown by haematoxylin and eosin staining.
Fig. 3. Clinical data of case 2. After three courses of methylprednisolone pulse therapy and subsequent tapering of prednisolone to 15 mg/day, severe drug eruption developed. 

- **a** Scattered erythematous plaques appeared on the trunk during the early disease period.
- **b** Biopsy revealed vacuolar degeneration of basal cells, admixed with individual cell necrosis and lymphocytic infiltration at the dermal-epidermal interface.
- **c** Membranous desquamation suggestive of epidermal necrosis during the regression period.