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Invited Review Article

Drug allergy and non-HIV immune reconstitution inflammatory syndrome

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ABSTRACT

Non-HIV immune reconstitution inflammatory syndrome (non-HIV IRIS) is associated with the recovery from an immunocompromised condition. It is defined as inflammatory disorders caused by antigens, including drugs or pathogenic microorganisms present prior to immune recovery, or by the exacerbation of an inflammatory disorder that was already present. Drug-induced hypersensitivity syndrome is a prototype of IRIS, and the pathophysiology of non-HIV IRIS can be recognized in several disorders treated with corticosteroids, immunosuppressants, molecular-targeted drugs, TNF- α antibody drugs, immune checkpoint inhibitors, and dipeptidyl peptidase-4 inhibitors. This review focuses on the relationship between the immune mechanism of non-HIV IRIS and drug allergies, especially severe drug eruption. The antigen recognition mechanism in drug allergy varies depending on the clinical type and the causative drug. The p-i concept is the main mechanism in severe drug eruption such as Stevens-Johnson syndrome/toxic epidermal necrolysis, and drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms. Lymphocytes activated by an antigen other than a drug, such as a virus, can also develop drug allergy by the loose binding of drugs with immune receptors of T cells or human leukocyte antigen. Therefore, fluctuations in the immune environment affect the onset of severe drug eruption. Novel agents that cause major changes in immunity have been marketed mainly for autoimmune diseases and malignant tumors; therefore, it is necessary to consider their effects when treating severe drug eruptions. Moreover, although a list of diagnostic criteria for this syndrome has been drafted, predictive and diagnostic biomarkers for this syndrome needs to be urgently developed.

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Concept and diagnostic criteria of non-HIV IRIS

The immune reconstitution inflammatory syndrome (IRIS) is a pathological condition involving the rapid exacerbation of infectious diseases that have already occurred or the appearance of new infectious diseases caused by latent viruses, *Mycobacteria*, fungi, and other pathogenic microorganisms. This condition is initiated after antiretroviral therapy (ART) in immunodeficient patients with HIV and results due to the restoration of immune function, including CD4-positive T lymphocytes.¹ When the immune system recovers, it activates an appropriate immune response against pathogenic microorganisms to resolve the infection. However, in

the case of IRIS, an excessive and violent immune response occurs that destroys normal tissues, resulting in severe and irreversible consequences. The target antigens may not be limited to pathogenic microorganisms but may include self-antigens due to the development of autoimmune disease.¹

The awareness of HIV infection has increased in recent years leading to its early detection and treatment. Since in such cases ART is performed before the onset of immunodeficiency in patients with HIV, the number of typical IRIS cases is decreasing. Instead, in addition to conventional immunosuppressants including corticosteroids, opportunities to use novel immunomodulators such as molecular-targeted agents, and checkpoint inhibitors that target some immune functions have been increasing.

The pathophysiology of IRIS that is not related to HIV infection are increasing; this has been reported by case reports and reviews globally.^{2–6} We have designated it as “non-HIV IRIS” and proposed a draft of diagnostic criteria (Table 1).⁷ The primary conditions

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underlying non-HIV IRIS are: (i) severe diseases such as collagen and autoimmune disease, (ii) severe drug eruptions such as drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms (DIHS/DRESS) in which immunosuppressive drugs, including corticosteroids, molecular-targeted drugs, and antibodies are used for treatment, (iii) malignant advanced-stage tumors, and (iv) pregnancy.⁵ The triggers that bring about non-HIV IRIS include the abrupt discontinuation and dose reduction of corticosteroids and immunosuppressive drugs, discontinuation and reduction of efficacy of biologics, especially anti-TNF- α antibodies,⁸ use of immune checkpoint inhibitors (ICIs), and childbirth.⁵ Although target antigens are often unknown but may include foreign antigens, such as latent pathogenic microorganisms and drugs, and self-antigens.^{2,4,7} Further, conditions that develop as non-HIV IRIS are predominantly infectious diseases, but also include autoimmune diseases such as type 1 diabetes and autoimmune thyroiditis, and severe drug eruptions, including Stevens-Johnson syndrome and toxic epidermal necrolysis⁹ (Fig. 1).

Novel classification of drug allergies by antigen recognition mechanism and IRIS

The mechanism of drug allergy has traditionally been explained by the “hapten hypothesis”. This hypothesis states that low molecular weight drugs bind to peptides, which are recognized as antigens by the antigen-presenting cells, and then they develop a drug-antigen specifically through the process of sensitization and induction.¹⁰ However, recent studies by Pichler have shown that the drug binds loosely to T cell receptors and human leukocyte antigen (HLA), and they can directly activate the T cells without sensitization, namely through immunological memory.¹¹ This concept has been referred to as the pharmacological interaction (p-i) concept.¹¹

The development of drug allergy according to the p-i concept is thought to be influenced by immune fluctuations such as IRIS. Drugs that did not develop drug eruption even after being

administered for a relatively long duration can develop drug eruption by activating T cells when the immune function is restored. Thus, drug eruption is considered to occur as an IRIS. Moreover, another mechanism for the development of drug allergy is the “altered peptide repertoire hypothesis”, when the drug binds to the HLA of antigen-presenting cells and changes the peptide structure, which activates the T cells.¹² Pichler suggested that different drugs have different antigen recognition mechanisms.¹³ For instance, the development of β -lactam antibacterial-induced drug allergies may follow either the hapten concept or the p-i concept.¹³ Anticonvulsants such as carbamazepine and allopurinol, which is often the causative agent of Stevens-Johnson syndrome (SJS) toxic epidermal necrolysis (TEN), follows the p-i concept.¹³ In contrast, abacavir¹⁴ and diaphenylsulfone¹⁵ follow the altered peptide repertoire mechanism (Table 2).

Drug-induced hypersensitivity syndrome as non-HIV IRIS

DIHS/DRESS is a severe drug eruption that causes lesions in various organs, in addition to the rash, fever, lymphadenopathy, and liver injury. Conventionally, it was known as anticonvulsant hypersensitivity.¹⁶ However, in 1998, two groups from the Kyorin and Ehime University revealed that the human herpesvirus 6 (HHV-6) was reactivated during the course, and the terminology of DIHS was introduced.^{17,18} Alternatively, the European groups used the terminology “drug reaction with eosinophilia and systemic symptoms (DRESS)” for the same condition because it was accompanied by systemic symptoms and eosinophilia.¹⁹ Hence, at present, this condition is internationally referred to as DIHS/DRESS.

Within two months of its onset, DIHS/DRESS is prone to develop fulminant type 1 diabetes, while within six months of its onset it may cause infectious diseases such as cytomegalovirus (CMV) reactivation, CMV infection, and *Pneumocystis jirovecii* induced pneumonia. Moreover, within three years of the onset of DIHS/DRESS, thyroid disease and hair loss may occur, followed by autoimmune diseases such as vitiligo vulgaris, systemic lupus erythematosus, systemic sclerosis, and autoimmune hepatitis. The polyglandular autoimmune syndrome may occur in the later phase, within 10 years after the onset of DIHS/DRESS²⁰ (Fig. 2). Furthermore, DIHS/DRESS may be associated with multiple autoimmune diseases simultaneously. For instance, we encountered a case of DIHS associated with fulminant type 1 diabetes mellitus with anti-GAD antibody, Hashimoto's disease with anti-thyroglobulin antibody, and alopecia (Lee *et al.*, submitted).

The pathophysiology of DIHS/DRESS is similar to that of IRIS, which occurs with the recovery of immunity from the immunosuppressive state caused by long-term oral administration of the culprit drug.² Evidence suggests that DIHS is a prototype of non-HIV IRIS.² For instance, (i) even if the culprit drug was discontinued, skin symptoms and hepatic dysfunction worsened,² (ii) in 9 out of 10 cases of DIHS, the number of CD4-positive T cells increased in the early stage of onset, and gradually decreased to the normal value two months after the onset,²¹ (iii) blood immunoglobulin such as IgG decreases at the early stage of onset and then recovers to the normal range,²² (iv) peripheral blood regulatory T cells (Treg) increase at the time of onset, but with the recovery of clinical symptoms due to drug discontinuation, the Treg regresses,²³ and a shift to Th17 occurs over a long period through the patrolling monocytes,²⁴ (v) the drug-induced lymphocyte stimulation test/lymphocyte transformation test of the culprit drug is often negative in the early stage of onset, but when the eruption is relieved, the positive rate increases as the immune response recovers.²⁵ In addition to the above-described immunopathogenesis of DIHS, recovery of the immune response by tapering of steroids may trigger the onset of often life-threatening infectious diseases

Table 1
Concept and draft diagnostic criteria of non-HIV IRIS.⁷

Concept
We studied the clinical courses of inflammatory disorders of various organs triggered by pre-existing antigens and pathogenic microorganisms. We included disorders that developed over several months, those that had recently manifested, and those that were already being treated but that clearly worsened upon recovery of HIV-negative patients from immunocompromised conditions.
Essential criteria (required)
1. HIV-negative;
2. The disorder was associated with recovery from an immunocompromised condition.
3. (1) The inflammatory disorder was caused by an antigen (including a drug) or a pathogenic microorganism present prior to immune recovery (unmasking); or, (2) exacerbation of an inflammatory disorder that had already developed or was being treated (a paradoxical disorder); or both (1) and (2).
Exclusion criteria
1. Exacerbation of primary disease after appropriate treatment.
2. Relapse/exacerbation of primary disease attributable to withdrawal of effective treatment.
3. An inflammatory disorder attributable to a newly ingested antigen or pathogenic microorganism after recovery from the immunocompromised condition.
Supportive findings
1. Multiple inflammatory disorders may develop simultaneously or sequentially.
2. Primary diseases include severe cutaneous adverse drug reactions such as drug-induced hypersensitivity syndrome; autoimmune, collagen, and related diseases; malignant tumors; and pregnancy.
Diagnosis
If a condition met all inclusion and exclusion criteria, that condition was considered to be non-HIV immune reconstruction inflammatory syndrome.

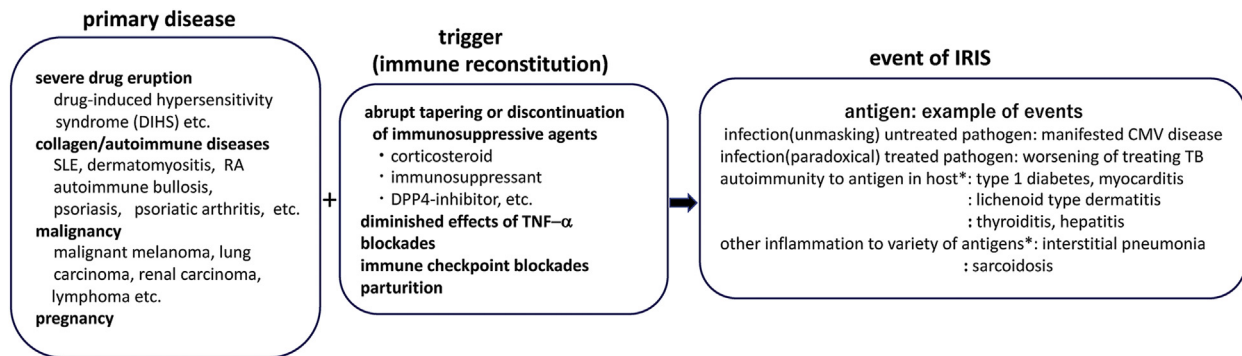


Fig. 1. Primary disease, trigger, and events of non-HIV IRIS. *It is difficult to clearly divide the target antigen into self (endogenous), non self (extrinsic). RA, rheumatoid arthritis; TB, tuberculosis.

such as CMV reactivation/infection, pneumonia, myocarditis, intestinal bleeding, and systemic bacteremia, and also autoimmune diseases.^{21,26–29} For this reason, the DIHS treatment guidelines clearly state that pulse therapy with steroids and sudden dose reduction should be avoided to prevent the onset of IRIS.³⁰ Administration of intravenous immunoglobulin also restores immunity and can trigger the onset of IRIS events; thus, it should be avoided in the treatment of DIHS.³⁰

Furthermore, the risk of developing IRIS is evaluated at an early stage of DIHS/DRESS onset, and while rapid dose reduction of corticosteroids is possible for mild cases, slower dose reduction should be done for severe cases.³¹ Mizukawa *et al.* proposed the DIHS/DRESS severity score and recommended that the indication and dose reduction rate of corticosteroid administration should be selected based on this score.³¹

Reactivation of HHV-6 is confirmed by HHV-6 variant B DNA detection in whole blood 2–3 weeks after onset of DIHS.³² Following reactivation of HHV-6, the Epstein–Barr virus, CMV, and the varicella-zoster virus may be reactivated.³² HHV-6 and CMV are also reactivated in patients without corticosteroids. CMV reactivation is involved in fatal diseases such as gastrointestinal bleeding, myocarditis, and pneumonia, and is greatly involved in treatment and prognosis.^{21,33} CMV reactivation commonly occurs between 4 and 6 weeks after the start of treatment for DIHS. In particular, since it is likely to occur around three days after the dose reduction of steroids, it is considered that CMV reactivation is a non-HIV IRIS accompanying the change in the immunological balance due to the dose reduction of corticosteroids.²⁹ Upon CMV reactivation, it is recommended not to change the dose of steroids, and to continue administration of antiviral agents such as ganciclovir until the antigenemia is completely relieved.³⁰ Scores that predict CMV reactivation in DIHS/DRESS from an early stage have been proposed and CMV reactivation can be predicted in the pre-treatment stage.³¹

In recent years, neutrophil-to-lymphocyte ratios (NLRs) in peripheral blood have been shown as predictive markers of prognosis and therapeutic effect in cancer patients. NLRs also serve as biomarkers for immune-related adverse events (irAE) due to immune checkpoint inhibitors³⁴ and various viral infections, including SARS-CoV-2 infection.³⁵ Matsukane *et al.* investigated whether NLR is useful as a predictive biomarker for the onset of irAE in cancer-bearing patients treated with anti-PD-1 antibodies.³⁴ Among the patients, NLR increased in the group with interstitial pneumonia from 4 weeks before the symptoms were observed.³⁴

Further, a comparison of NLR was made between the CMV positive and negative group at 2–4 weeks before the onset of DIHS/DRESS cases. The CMV-positive group had significantly higher NLR than the negative group (4.5 vs 2.1, $p > 0.01$, manuscript in

preparation), and the tendency was not affected by corticosteroid treatment. NLRs also increased rapidly over time in severe cases of DIHS/DRESS, consistent with CMV antigenemia and severe type 1 diabetes (Lee *et al.*, submitted). Hence, NLR could be a useful biomarker for predicting or diagnosing the onset of various non-HIV IRIS, including CMV reactivation.

Moreover, serum cytokines could also predict the risk of CMV infection in DIHS. Serum levels of IL-10 > 80.9 pg/mL, and if it is less than that, IL-8 > 34.2 pg/mL, IL-12p40 > 6.8 pg/mL, and IL-15 > 6.2 pg/mL were proposed as the mark for the risk of CMV infection.³⁶ It has been reported that the onset of CMV infection (including reactivation) has a sensitivity of 88.9% and a specificity of 100% when these criteria were met.

SJS/TEN that develops as an IRIS event

Most of the severe cutaneous adverse drug reactions (SCAR) such as SJS/TEN are life-threatening and may leave sequelae in the eyes and respiratory organs. Antigen recognition in SCAR is caused preferentially by the p-i concept.¹¹ Therefore, the immune environment that affects the activation of cytotoxic T cells may boost the onset of SCAR. According to the Euro SCAR survey, corticosteroids were administered before onset in 14.8% of 379 SJS/TEN cases and was considered to be a high-alert drug for SJS/TEN.³⁷ In the SJS/TEN nationwide epidemiological survey conducted in Japan during 2016–2018, corticosteroid administration before the onset of SJS/TEN was 15.6% (68 out of 437 cases), which was close to the rate reported in the Euro SCAR survey.³⁸ When comparing the group with corticosteroid administration before SJS/TEN versus the group without it, the group with corticosteroid was older, had more TEN than SJS, a low frequency of high fever, and the suspected drug has a higher proportion of antibacterial agents and a higher mortality rate. These characteristics were statistically significant (unpublished data). The incidence of SJS/TEN onset following a maximum steroid dose and tapering of steroid dose were almost similar, although there was no evidence that it developed as IRIS associated with corticosteroid tapering (unpublished data).

A study investigating changes in Tregs due to steroid pulse therapy in multiple sclerosis reported an increase in Tregs and IL-10 48 h after the end of pulse therapy and returned to pre-treatment levels 6 weeks after the end of pulse therapy.³⁹ Indeed, in patients with systemic lupus erythematosus and immune thrombocytopenic purpura, corticosteroid exert therapeutic effects by inducing an increase in the percentage of Treg subsets.⁴⁰ Furthermore, a strong correlation between Treg cell percentage and corticosteroid dose has been demonstrated.⁴⁰ Hence, the presence of collagen disease or autoimmune disease, and the fluctuation of immunity due to the administration of corticosteroids and its

Table 2
List of drugs associated with classification of drug-allergy.¹³

Hapten	p-i	Pseudo-allergy
β-lactam antibiotics: penicillin, flucloxacillin, amoxicillin, cephalosporins, monobactam	β-lactam antibiotics: flucloxacillin, amoxicillin, cephalosporins, monobactam	NSAIDs: acetylsalicylic acid, diclofenac, mefenamic acid, ibuprofen, etc.
Sulphanilamides: sulphamethoxazole	Sulphanilamides: sulphamethoxazole	Quinolones
Quinolones	Quinolones	Quinolones
Non-ionic iodinated radiocontrast media	Non-ionic iodinated radiocontrast media	Non-ionic iodinated radiocontrast media
Muscle relaxants: (rocuronium, suxamethylcholin, etc.)	Muscle relaxants: (rocuronium, suxamethylcholin, etc.)	Muscle relaxants: (rocuronium, suxamethylcholin, etc.)
	Vancomycin	Vancomycin
	Antiepileptics: carbamazepine, lamotrigine, phenytoin	
	Local anesthetics: lidocaine mepivacaine	
	Allopurinol/oxypurinol	

tapering may affect the onset of SJS/TEN, which warrants further investigation.

There was one case each of SJS and TEN that developed during steroid tapering after multiple steroid pulse therapies for Vogt-Koyanagi-Harada disease.⁹ Although there was no high fever, the onset seemed mild, epidermal necrosis progressed thereafter. The culprit drug, H2 blockers and proton pump inhibitors, was unlikely to be the causative agent of severe drug eruption and the causative agent could not be determined.

Similarly, Figure 3 shows a case of herpes zoster followed by SJS during treatment with corticosteroids for dermatomyositis. The case was of a woman in her 80s who was diagnosed with dermatomyositis due to swelling of the fingers, muscle weakness, and rash on the face and dorsa of the hand. Herpes zoster developed in the area of the first branch of the trigeminal nerve, and acyclovir and acetaminophen were administered. Herpes zoster improved 14 days later, and the prednisolone was reduced from 25 mg/day to 20 mg/day. Erythematous plaques developed from the relief area of herpes zoster and spread to the face and trunk, accompanied by conjunctive congestion and extensive erosion of the lips (Fig. 4).

More cases of SJS/TEN associated with collagen disease in Japan from 2012 to 2015 are summarized in Table 3. It is noteworthy that two cases were of pregnant women and two cases were of patients with tuberculosis; in the latter case, isoniazid was included in the culprit drug.

Pregnancy is prone to IRIS.⁵ The Treg expands from early to mid-pregnancy, and the immune response to the fetus and the excessive immune response to pathogenic microorganisms are suppressed, contributing to the continuation of pregnancy.⁴¹ However, from late pregnancy onwards, especially after delivery, Tregs shrink in parallel to hormonal dynamics, and Th1-dominant immune function is restored.⁴¹ It is thought that this causes IRIS events such as the aggravation of infectious diseases against latent pathogenic microorganisms such as tuberculosis,⁵ the exacerbation of autoimmune diseases, psoriasis⁴² and the onset of SJS/TEN.⁹

Tuberculosis patients with extrapulmonary infection during pregnancy account for 5–10% of IRIS development, but it has been reported to reach 93% after delivery.⁵ Autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, and multiple sclerosis also improve with a decrease in Th17/Treg during pregnancy and worsen with an increase in Th17/Treg postpartum.⁴¹

DPP4 inhibitor-related bullous pemphigoid as non-HIV IRIS

The dipeptidyl peptidase-4 inhibitors (DPP-4i) do not provoke hypoglycemia, weight gain or cardiovascular events, and are relatively free from adverse side effects.⁴³ Hence, DPP4i is frequently used as general internal medicine in Japan. DPP-4, also known as

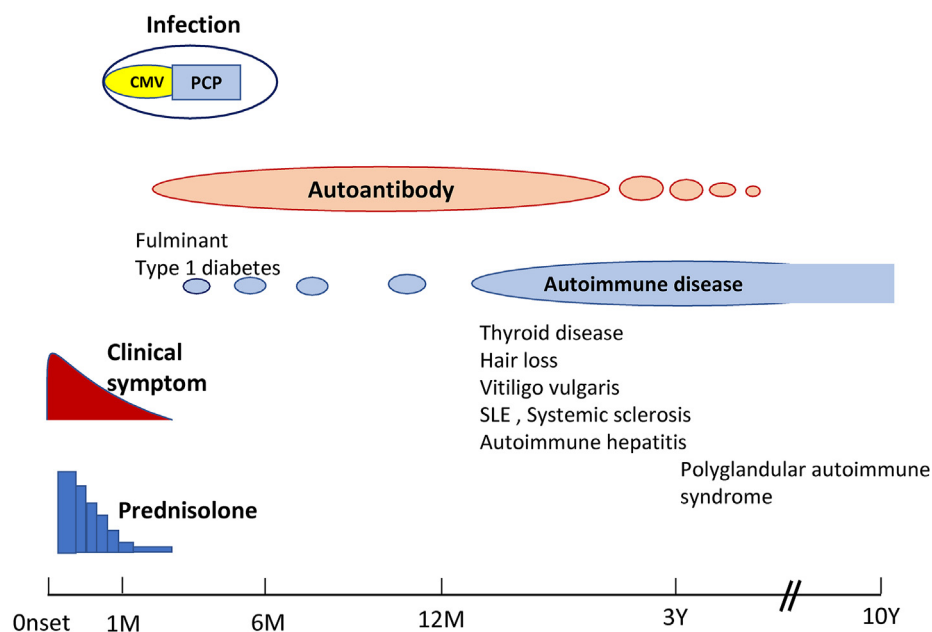


Fig. 2. Infectious-IRIS and autoimmune-IRIS during the long-term course of DIHS/DRESS. PCP, Pneumocystis pneumonia.

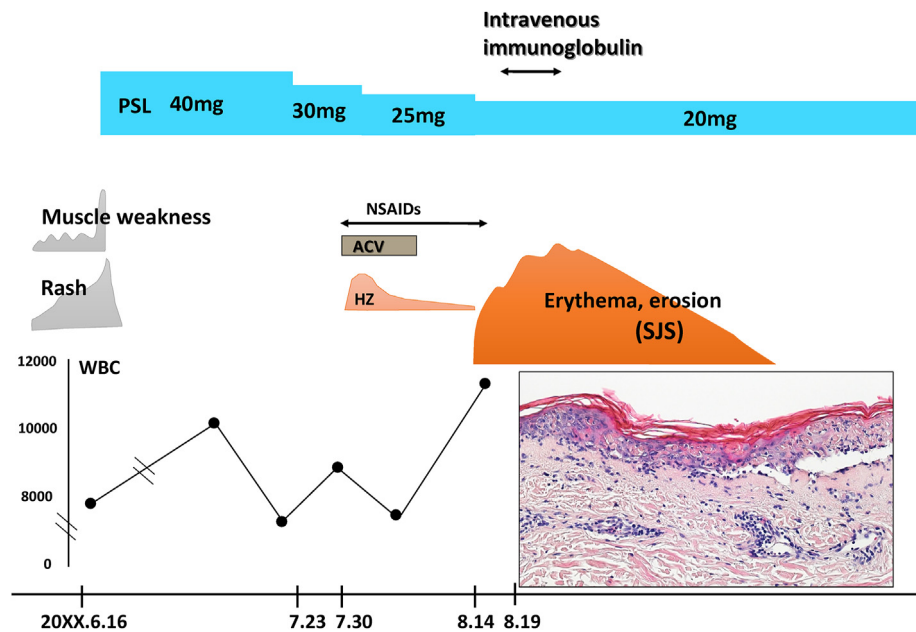


Fig. 3. Clinical course of dermatomyositis treated by corticosteroids where herpes zoster and subsequent SJS developed as non-HIV IRIS.



Fig. 4. Clinical features of SJS. Erythematous plaques with erosions developed from the relief area of herpes zoster and spread to the face and trunk, accompanied by conjunctive congestion and extensive erosion of the lips.

CD26, is expressed on the surface of activated immune cells such as T cells.^{44,45} Long-term oral administration of a DPP-4i exerts an immunosuppressive effect.⁴⁴ Hence, the onset or worsening of inflammatory diseases associated with immune recovery due to the discontinuation of DPP4i can be understood as an IRIS.^{4,7} In the field of dermatology, patients receiving DPP-4i often experience bullous pemphigoid, an autoimmune bullous disease that targets type XVII collagen.⁴⁶ In some cases, the discontinuation of DPP-4i spontaneously improved bullous pemphigoid without systemic administration of corticosteroids. However, there are cases in which bullous pemphigoid worsens after discontinuation and is complicated by additional infection, thereby requiring systemic corticosteroid therapy; in such cases, it is considered to be an immunological mechanism of IRIS.

Sugiyama *et al.* followed patients for more than 90 days after discontinuation of DPP-4i, and retrospectively compared patients who achieved spontaneous remission after discontinuation of DPP-4i (remission group, N = 8) with those showing exacerbated bullous pemphigoid and requiring systemic corticosteroids (exacerbation group, N = 9).⁴⁷ The neutrophil-to-lymphocyte ratio of peripheral blood was examined as a predictive biomarker for the prognosis of bullous pemphigoid, with the baseline set to values before DPP4i discontinuation. The cutoff value of NLR was 4.30 at baseline and 6.58 at the peak. An NLR above 6.58 suggested a worsening of condition after DPP4i discontinuation, and those cases required a systemic administration of steroids.⁴⁷ Viral and bacterial infections (infectious-IRIS) also developed in patients who showed a marked increase in NLR after discontinuation of DPP-4i.⁴⁷ There was no recurrence of bullous pemphigoid within one year in the remission group. In the exacerbation group treated with systemic corticosteroids, bullous pemphigoid was relieved by day 60, but only two cases achieved complete discontinuation of corticosteroid (after 603 days and 1165 days of treatment).⁴⁷ Although the number of cases was insufficient, it was shown that the exacerbation group resulted in a lower survival rate than that in the remission group, since four people died due to infectious IRIS within a year in the corticosteroid-treated exacerbation group.⁴⁷

Drug-allergy as irAE

In this review, we considered ICI-induced irAE as a part of the non-HIV IRIS, and research is ongoing from this perspective. However, although irAE meets the diagnostic criteria of non-HIV IRIS proposed before, there are differences in the mechanism of immune function recovery. For instance, IRIS is triggered by the discontinuation, dose reduction, or diminished effect of immunosuppressive agents, while irAE is induced by ICIs targeting PD-1, PD-L1, and CTLA-4.⁷ Although there are several identical diseases between IRIS and irAE events in DIHS, there are differences in the timing and frequency of their onset.⁷ In cases of DIHS, infectious diseases such as CMV and *P. jirovecii* infection often occur within three months after the onset, followed by the appearance of autoantibodies and the onset of autoimmune diseases sporadically.

Table 3
Reported cases of SJS/TEN associated with collagen disease in Japan during 2012–2015.

Case No.	Age	Gender	Primary disease	Culprit drug	Onset of SJS/TEN
1	3	M	Kawasaki disease	unknown	2 weeks after IVlg
2	58	F	dermatomyositis	Isoniazid, Rifampicin	10 days after tapering betamethasone to 5 mg/day under treatment for tuberculosis
3	24	F	SLE	acetaminophen	28 days after tapering PSL to 11 mg/day, (pregnant 27th week)
4	48	F	SLE	Isoniazid	6 weeks after tapering betamethasone under treatment for tuberculosis
5	24	F	SLE	acetaminophen	PSL 30 mg/day, pregnant
6	82	F	dermatomyositis	acetaminophen	One day after tapering PSL to 20 mg/day, after herpes zoster

over a long period of time.⁴⁸ However, in cases of irAE, infectious diseases common to IRIS are occasionally found, but many autoimmune diseases such as colitis, hypophysitis, type 1 diabetes, and autoimmune thyroiditis occur from an early stage.⁴⁹

Treg dysfunction is assumed to be a common mechanism for IRIS and irAE. The reasons include: (i) immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome with a mutation in the *FOXP3* gene shows Treg deficiency that is also

observed in irAE and IRIS, and several autoimmune diseases are common to IPEX syndrome, irAE, and IRIS.⁵⁰ (ii) Tregs are significantly reduced even in animal models of irAE.⁵¹

Skin disorders also occur during irAE. Among these disorders, some cases are considered to be drug eruptions.⁵² A Japanese group working on SCAR analyzed 179 events of irAE in 163 cases of skin disorders due to ICIs.⁵² Additionally, in 60 cases of lung cancer, the incidence of lichenoid eruption (Fisher's exact test, $p = 0.017$) and localized erythema (Fisher's exact test, $p = 0.0195$) was significantly higher than that of other malignancies.⁵² The lichenoid reaction, an irAE, is a relatively frequent skin disorder, accounting for approximately 17% of patients using anti-PD-1 antibody.⁵³ The reason behind why lichenoid eruption is significantly observed in lung cancer is unknown. T cells activated by ICIs are also expressed in the basal layer of the epidermis for some reason,⁵⁴ and they react to self-antigens. There were no other significant types of drug eruption, but disseminated maculopapular and psoriasis-like eruptions were more common. The frequency of leukoderma was significantly higher in malignant melanoma,^{52,55} while the frequency of disseminated maculopapular eruption was significantly higher in head and neck cancer and renal cell carcinoma.⁵²

Eighty per cent of patients with lichenoid reactions have a history of oral medications that cause lichenoid reactions, such as calcium channel blockers and anti-aldosterone, and ICIs can activate T cells even in previously tolerant patients.⁵⁴ Even an antihypertensive agent taken for a long time before ICI administration was considered to be a suspected drug. When discontinuation of the suspected drug alleviates the skin disorder even if ICI is continued, or re-administration of the suspected drug induces skin symptoms, the suspected drug could be the culprit drug.

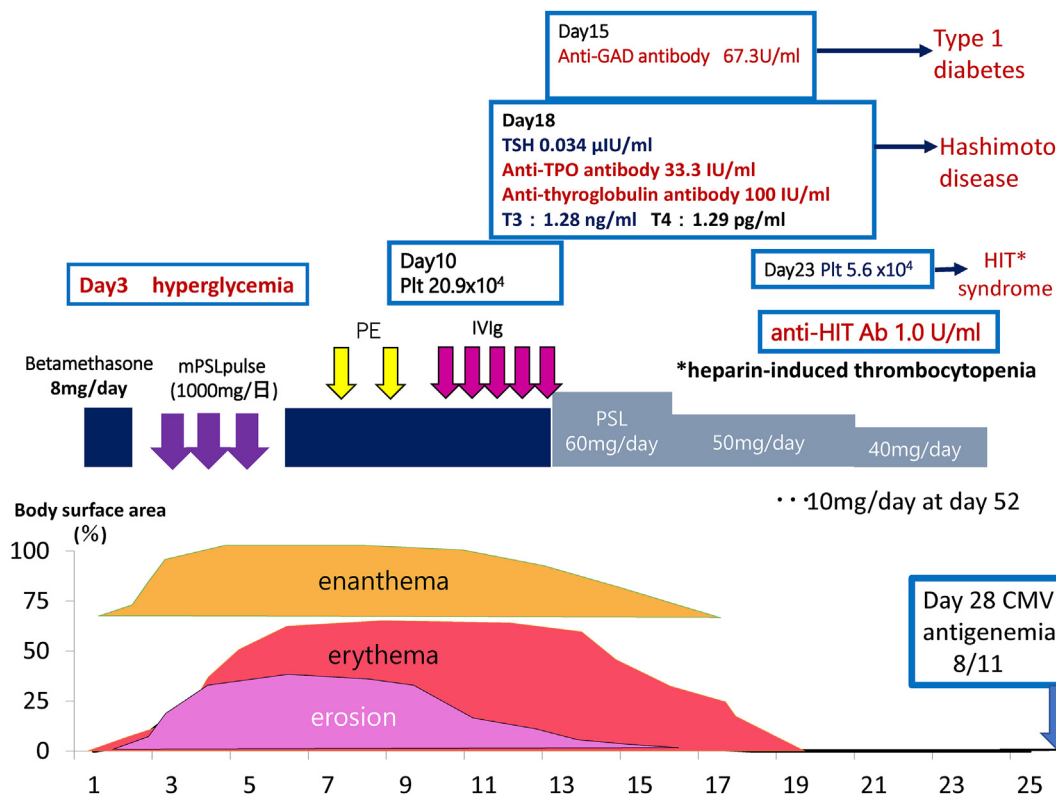


Fig. 5. A case of TEN that developed as irAE. During the course of TEN, autoimmune diseases such as anti-glutamic acid decarboxylase antibody-positive type 1 diabetes occurred on the 15th day, Hashimoto's disease on the 18th day, heparin-induced thrombocytopenia syndrome with heparin associated antibody on the 23rd day, and finally CMV antigenemia on the 28th day.

In a study, 22 patients and 24 events were suspected of being involved in the onset of skin disorders other than ICI itself. The suspected drugs consisted of six antimicrobials, five anti-inflammatory analgesics, two cyanamides, two lansoprazoles, and two allopurinols, with an average onset time of 114.6 days.⁵² It is not easy to prove that ICIs cause or exacerbate drug allergies, but it is important to always consider the possibility of drug eruption caused by coexisting drugs.

Furthermore, a small number of cases of SJS/TEN that developed as irAE have been reported.^{56–58} One of the most severe cases of TEN was a woman in her 60s, who was given nivolumab for six months with advanced oral melanoma, but it was discontinued because of the worsening of conditions. The patient developed TEN a month later. The patient was taking acetaminophen, an antibacterial drug, and famotidine shortly before onset.⁵⁶ During the course of TEN, autoimmune diseases such as anti-glutamic acid decarboxylase antibody-positive type 1 diabetes appeared on the 15th day, Hashimoto's disease on the 18th day, heparin-induced thrombocytopenia syndrome with heparin associated antibody on the 23rd day, and finally CMV antigenemia on the 28th day. Drug-induced lymphocyte stimulation test/lymphocyte transformation test of the coexisting drug was positive. Collectively, it was speculated that the immunomodulation triggered by nivolumab caused drug allergy and led to the onset of TEN (Fig. 5).⁵⁶ At the onset of TEN, Treg (%), *FOXP3* mRNA expression, and CD4/CD8 decreased, whereas serum IL-6, IL-9, IL-12, IL-17, IFN- γ and GM-CSF increased compared to before the start of nivolumab.⁵⁶ The transition of these cytokines is interesting because they have much in common with the sequential changes of cytokines when multiple autoimmune diseases occur as IRIS that we have encountered in the case of DIHS (Lee et al., submitted). Hence, we would like to examine biomarkers common to irAE and IRIS by accumulating cases in the future.

Conclusion and future direction

This review focuses on the relationship between the immune mechanism of non-HIV IRIS and drug allergies, especially severe drug eruption. Since antigen recognition in most severe drug eruptions such as SJS/TEN and DIHS/DRESS follows the p-i mechanism, fluctuation in the immune environment by corticosteroids, molecular targeted agents, and immunomodulators including ICI has an immense effect on the onset and severity of drug eruption.

Events that are considered non-HIV IRIS are often encountered in routine practice, but the lack of quantitative criteria does not clarify to what extent it should be diagnosed as IRIS. Hence, there is an urgent need to develop biomarkers for diagnosis and biomarkers predicting the onset of IRIS.

In cases of infectious diseases as an event of non-HIV IRIS, antibacterial therapy against the causative microorganism, in combination with corticosteroids or immunosuppressive agents to suppress the hyperimmune response, is necessary.⁵⁹ In addition, TNF- α inhibitors,² anti-IL-6 antibodies, Statin preparations,⁶⁰ among others are listed as candidates for therapeutic agents against non-HIV IRIS, and future trials are awaited. Hence, comprehensively analyzing different cases, it is essential to arrive at a clinical decision with the concept of non-HIV IRIS in mind when treating drug allergies, especially severe drug eruptions.

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Conflict of interest

The authors have no conflict of interest to declare.

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