DERMATOLOGICA SINICA 31 (2013) 211–216

Contents lists available at ScienceDirect

Dermatologica Sinica

journal homepage: http://www.derm-sinica.com

REVIEW ARTICLE

Long-term outcome of patients with severe cutaneous adverse reactions

Yoko Kano*, Tetsuo Shiohara

Department of Dermatology, Kyorin University School of Medicine, Mitaka, Tokyo, Japan

ARTICLE INFO

Article history:
Received: Jul 16, 2013
Revised: Sep 5, 2013
Accepted: Sep 24, 2013

Keywords:
drug eruption
drug-induced hypersensitivity syndrome
drug reaction with eosinophilia and systemic symptoms
sequela
Stevens-Johnson syndrome
toxic epidermal necrolysis

ABSTRACT

Visceral involvement associated with Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) and drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms (DIHS/DRESS) is well documented. However, little is known about the long-term outcomes of severe drug eruptions due to a lack of long-term follow-up. Long-term sequelae may arise in patients who survive the acute complications of severe drug reactions. In SJS/TEN, extensive scarring that result from the healing of mucocutaneous ulcerative lesions may interfere with organ function. Severe sequelae include visual impairment and pulmonary obliterative disease that impair patients' quality of life. In DIHS/DRESS, recent observations suggest that fulminant type 1 diabetes mellitus (FT1D) and autoimmune diseases such as autoimmune thyroiditis and lupus erythematosus can occur after a disease-free period of several months to years. Thus, DIHS/DRESS may lead to the development of autoimmune diseases, which may be overlooked. Dermatologists need to be aware of the sequelae that may arise following resolution of severe cutaneous adverse reactions and should be vigilant for manifestations of autoimmune disease during follow-up.

Introduction

Severe cutaneous adverse eruptions include Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) and drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms (DIHS/DRESS). Visceral involvement can occur during the course of these diseases, including sepsis and pneumonitis in SJS/TEN, and hepatitis and renal failure in DIHS/DRESS. However, the long-term sequelae after resolution of severe drug eruptions is not well known, due to the lack of long-term follow-up and the potential development of sequelae after a disease-free period of several months to years. As there is limited information on the long-term outcomes of severe drug eruptions,[1–3] we present a review on the long-term outcomes of SJS/TEN and DIHS/DRESS.

Sequelae in SJS/TEN

SJS/TEN are rare, potentially life-threatening conditions triggered by drug administration and infections.[4,5] SJS and TEN are now recognized as variants of the same condition with differing severities. Although the pathomechanism of epidermal necrosis in SJS/TEN remains unknown, various factors have been implicated, including drug-specific T cells and/or monocytes/macrophages,[6] regulatory T cell function,[7,8] Fas/Fas ligand and perforin/granzyme B,[9] pro-inflammatory cytokines,[10,11] and granulysin produced by natural killer cells.[12] The skin and mucous membrane are affected in SJS/TEN, and mucosal involvement can be more severe than cutaneous involvement. Healing of ulcerative mucosal lesions may result in extensive scarring that interferes with organ function. Ocular and dermatologic long-term sequelae may occur and affect patients' quality of life, emphasizing the need for long-term follow-up of patients after resolution of SJS/TEN.

Ocular sequelae in SJS/TEN

Ocular sequelae in patients with SJS/TEN are well documented. The involvement of the ocular surface is very common and can result in long-term complications. In the acute disease, many patients experience mild to severe ocular involvement,[1] which include conjunctivitis and epithelial sloughing in mild cases, and pseudomembranous and membranous conjunctivitis and corneal and/or conjunctival epithelial defects with severe pain and photophobia in severe cases.[13] Inflammation of the ocular surface frequently persist

* Corresponding author. Department of Dermatology, Kyorin University School of Medicine, 6-20-2 Shinkawa, Mitaka, Tokyo 181-8611, Japan. Tel.: +81 422 47 5511; fax: +81 422 47 9632.
E-mail address: kano@ks.kyorin-u.ac.jp (Y. Kano).

1027-8117/$ – see front matter Copyright © 2013, Taiwanese Dermatological Association. Published by Elsevier Taiwan LLC. All rights reserved.
http://dx.doi.org/10.1016/j.dsi.2013.09.004

after complete resolution of cutaneous lesions, leading to ocular sequelae in chronic stage, at least 1 year from the onset of SJS/TEN. Even minor involvement of the ocular surface in the acute disease may lead to chronic ocular discomfort that requires long-term therapy.

The ocular sequelae are broadly classified into three categories depending on the involving area. Corneal sequelae include superficial punctate keratinopathy, epithelial defect, loss of the palisades of Vogt, conjunctivalization, neovascularization, opacification, and keratinization. Conjunctival sequelae include conjunctival hyperemia and symblepharon formation. Eyelid sequelae include trichiasis, mucocutaneous junction involvement, meibomian gland involvement, lacrimal gland and duct involvements, and punctal damage (Figure 1).[1] These lesions can cause prolonged ocular discomfort and visual impairment, and may require long-term therapy. Among ophthalmic problems, severe dry eye is the most common long-term ocular sequela and is present in approximately 50% of patients with SJS/TEN. Trichiasis is also a common ocular sequela. In particular, corneal involvement such as neovascularization, opacification, and keratinization correlates with visual acuity (Table 1).

With respect to possible causes, *Mycoplasma pneumoniae*-associated SJS induced more ocular involvement during the acute stage than drug-induced SJS. *Mycoplasma pneumoniae*-associated SJS seldom caused long-term ocular sequelae in children, while adult patients remained at risk for long-term sequelae.[14,15] Recent genotype analyses revealed that multiplicative interactions of human leukocyte antigen (HLA)-A and Toll-like receptor 3 (TLR3) genes might be required for the development of ocular complications in SJS/TEN.[16]

Table 1 Sequelae in SJS/TEN.

Ocular lesion
Cornea: superficial punctate keratinopathy, epithelial defect, loss of palisades of Vogt, conjunctivalization, neovascularization, opacification, keratinization
Conjunctiva: conjunctival hyperemia, symblepharon formation
Eyelid: trichiasis, mucocutaneous junction involvement, meibomian gland involvement, lacrimal gland and duct involvements, punctal damage
Mucocutaneous lesion
Urogenital system: vaginal obstruction/vaginal stenosis, vulvovaginal adenosis/endometriosis, urinary stream egress obstruction
Skin: pigmentary change, dry skin (xeroderma), appearance of melanocytic nevi or ectopic sebaceous gland, nail deformity
Pulmonary lesion
Obliterative bronchitis/bronchiolitis
Esophageal lesion
Stricture formation

SJS/TEN = Stevens-Johnson syndrome/toxic epidermal necrolysis.

Mucocutaneous sequelae in SJS/TEN

Despite documented involvement of the genitals in female patients with SJS/TEN, little information exists regarding long-term genital complications. Genital involvement during SJS/TEN includes erosive and ulcerative vaginitis, vulvar bullae, and vaginal synechiae.[17] Extensive scarring that affects genital function may occur with the healing of mucosal ulcerations.

Vaginal or vulvar areas of necrosis may form adhesions. Very few cases of symptomatic vaginal obstruction after SJS/TEN have been documented. Pathologic changes in the vulvovaginal area have been observed in women with SJS/TEN. Vulvovaginal adenosis/endometriosis—defined by the presence of metaplastic cervical or endometrial glandular epithelium within the vaginal wall—has been reported, causing dyspareunia and postcoital bleeding.[17] The cause remains unknown; it has been proposed that tubal or uterine epithelium implant over the raw areas during SJS/TEN.[18] The malignant potential of adenosis is unknown, but transformation to adenosis with cellular atypia of the vagina has been reported.[17] In a pediatric case, extensive labial synechiae and hydrocolpos occurred several years after an episode of SJS/TEN. Amenorrhea, cyclical abdominal pain, or a hypogastric mass in girls after an episode of SJS/TEN may indicate acquired vaginal obstruction. Thus, after a diagnosis of SJS/TEN in girls, it is prudent to schedule a prepubertal genital examination to avoid obstructed menstruation and future sexual problems.[18]

Several strategies to prevent vulvovaginal sequelae have been described. The application of intravaginal glucocorticoids, use of vaginal molds, and menstrual suppression during SJS/TEN have been proposed to reduce the formation of adhesions and limit metaplastic changes in affected areas.[17]

Other mucosal sequelae resulting from an obstructed urinary system include urinary retention and recurrent cystitis. Persistent lingual ulcerations and recurrent oral aphthae can be observed months after the resolution of SJS/TEN.[19]

Unlike mucous membranes, the skin usually heals within weeks without scarring if wounds are treated adequately. The development of hypertrophic scars in SJS/TEN has rarely been described in the literature.[20] Other cutaneous sequelae include dyspigmentation, nail deformity and fingernail loss, and xeroderma. It is likely that nail involvement is associated with ophthalmic involvement (Figure 2).[21] It is well known that Sjögren-like syndrome frequently

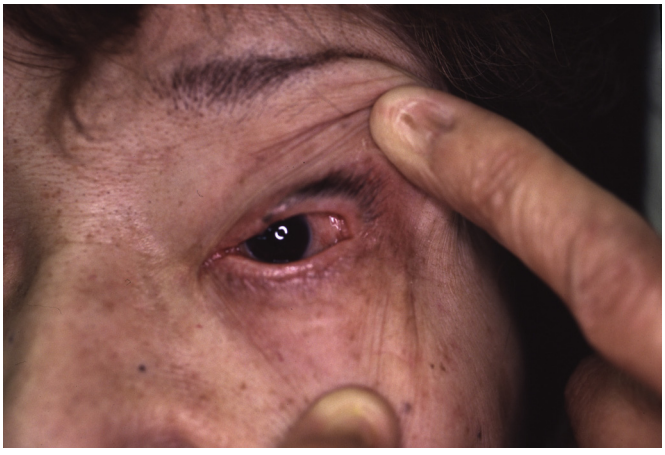

Figure 1 Blepharosynechia after resolution of toxic epidermal necrolysis (TEN).

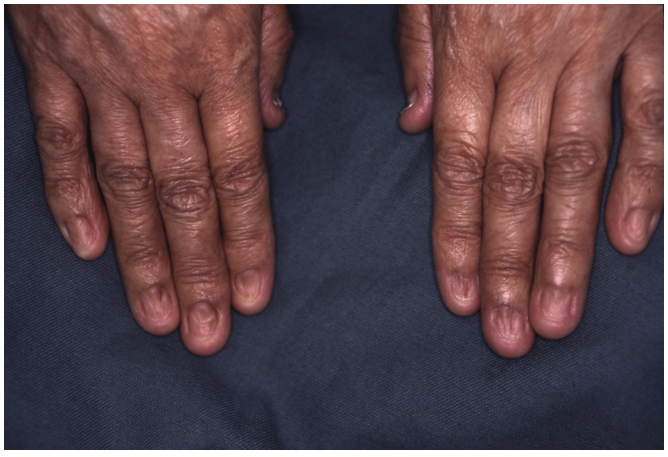

Figure 2 Nail loss after resolution of toxic epidermal necrolysis (TEN).

occurs after resolution of TEN.[22] Dry skin and heat intolerance are common complaints among survivors of SJS/TEN with involvement of the eccrine duct, although the secretory gland is usually normal.[23]

The sudden appearance of numerous melanocytic nevi following severe bullous lesions in a patient with SJS had been reported; it was speculated that the production of cytokines and growth factors during epidermal regeneration may have led to the proliferation of melanocytes.[24] In a separate case, widespread eruption of ectopic sebaceous glands occurred 4 months after an episode of SJS.[25] Similar to the aforementioned case, cytokines and growth factors were thought to be responsible for the proliferation of residual sebaceous gland cells.[25]

Pulmonary sequelae in SJS/TEN

The incidence of pulmonary involvement in SJS/TEN has not been examined. Pulmonary involvement in SJS/TEN is divided into two types: interstitial pneumonia during the course of SJS/TEN, and obliterative bronchitis/bronchiolitis after the resolution of SJS/TEN.[26] According to one report, pulmonary sequelae tend to occur in relatively young patients.[27] A few cases of obliterative bronchitis/bronchiolitis after SJS/TEN have been documented, as well as respiratory tract obstruction and bronchiectasis. The interval from the onset of SJS/TEN to development of pulmonary sequela is unclear because some reported cases show persistent respiratory symptoms from the onset of SJS/TEN.[27]

Obliterative bronchitis/bronchiolitis is diagnosed using imaging and respiratory function tests, with findings of bronchiectasis on high resolution computed tomography (CT) of the chest, occlusion of the bronchus on bronchoscopy, and a severe obstructive pattern in the flow–volume curve. Although the pathomechanism remains unknown, immunological pathways, infection, and remodeling of the bronchial mucosa are implicated in the pulmonary sequelae of SJS/TEN.

If patients suffer from recurrent respiratory symptoms after the resolution of SJS/TEN, they should be closely monitored using respiratory function tests and CT. No effective treatment is available for permanent obstructive pulmonary changes in obliterative bronchitis/bronchiolitis. In severe cases, mechanical ventilation is required, and living-donor lung transplantation may be necessary. Patients with pulmonary sequela after resolution of SJS/TEN tend to have a poor prognosis.

Esophageal sequelae in SJS/TEN

Long-term sequelae involving the gastrointestinal tract have rarely been reported. Esophageal stricture as a consequence of SJS has been reported in children but is rare in adults.[28,29] Two patients had foreign bodies lodged in esophageal strictures, occurring at 7 months after the episode of SJS in one case and at 18 months after the episode of SJS in the other case. The delay in the onset of dysphagia suggests that stricture formation may be subclinical. SJS/TEN-related esophageal stricture is thought to occur because of irritation caused by orally administrated medications, ingestion of coarse food, or nasogastric feeding during SJS/TEN. Esophageal strictures after SJS/TEN are easily dilated, suggesting that the condition is caused by injury to the esophageal mucosa without involvement of the muscularis.[29]

Sequelae in DIHS/DRESS

DIHS/DRESS is a severe adverse drug reaction caused by specific drugs such as anticonvulsants and allopurinol, and is characterized by visceral involvement and reactivation of human herpesviruses (HHV).[30–32] Various internal organs can be affected during the course of disease.[33–39] Furthermore, the development of autoimmune diseases several months to years after clinical resolution of DIHS/DRESS have been reported.[2,3] Several autoimmune diseases can develop sequentially in a single patient.[40] The emergence of autoimmune disease might be overlooked unless dermatologists perform long-term follow-up of patients after their recovery from DIHS/DRESS (Figure 3).[41]

Internal organ failure

Previous reports reveal that severe renal insufficiency increases the risk of mortality, and mortality depends in part on the degree of renal involvement rather than hepatic involvement.[41] Renal insufficiency following after acute interstitial nephritis at the acute stage of DIHS/DRESS could require a lifetime hemodialysis.[2] It is more likely to occur in elderly patients with pre-existing renal disease or those receiving diuretic therapy. Because renal function declines steadily with age, elderly patients are vulnerable to renal complications and sequelae.

Appearance of autoantibody after onset of DIHS/DRESS

Autoantibodies have been detected in patients with DIHS/DRESS after resolution of the disease. According to an analysis of 34 cases of DIHS/DRESS at our institution, autoantibodies such as antinuclear antibody (ANA), anti-thyroperoxidase (TPO), and anti-thyroglobulin antibodies were observed without any clinical manifestations.[3] The proportion of DIHS/DRESS patients with autoantibodies is higher than that seen in SJS/TEN patients.[42] The percentage of DIHS/DRESS patients with autoantibodies was higher in the group that received supportive treatment alone than those who received systemic corticosteroids.[3] The autoantibody titers fluctuated but remained elevated during the observation period. Our study showed that autoantibodies are present in some patients after clinical resolution of DIHS/DRESS without causing clinically overt diseases.

Autoimmune thyroid disease as a sequela in DIHS/DRESS

Thyroid disease is the most frequently detected sequela following the resolution of DIHS/DRESS, with a cumulative incidence of 3.8%. This incidence is more than 10-fold higher than the expected incidence of this disease in the Chinese population.[2] Endocrinologic evaluation of patients with DIHS/DRESS revealed thyroid gland abnormalities, such as increased free thyroxine (FT4), low thyroid-stimulating hormone (TSH), and elevated TSH levels, and production of autoantibodies, including anti-TSH receptor, anti-TPO, and anti-thyroglobulin antibodies. As symptoms are not usually observed, these abnormal findings may be missed if evaluation of thyroid function and antibodies are not performed.

Graves' disease may develop after the resolution of DIHS/DRESS. Recently, it has been reported that the interval between discontinuation of the causative drug and the onset of Graves' disease is approximately 2 months to 1 year. A recent case report described the appearance of a diffuse large thyroid goiter followed by hyperthyroidism 2 months after the onset of sulfasalazine-induced DIHS/DRESS.[43] Thyrotoxicosis can be the initial presenting symptom of thyroid disease.[44] Two patients diagnosed with Graves' disease with symptoms of hyperthyroidism and elevation in FT4 plus suppression of TSH have been documented—one case had symptoms 1 month after the onset of DIHS/DRESS while the other had symptoms 9 months after the onset of DIHS/DRESS.[2] Brown et al described a patient with Graves' disease confirmed by thyroid tests that developed 5 months after withdrawal of the causative

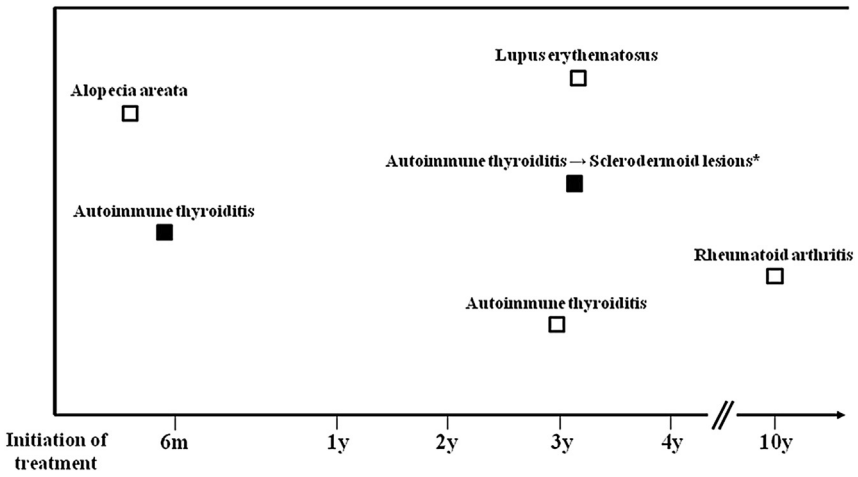

Figure 3 Autoimmune diseases developed after resolution of drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms (DIHS/DRESS). Six out of the 37 patients with DIHS/DRESS developed autoimmune diseases in our institution. The period of follow-up was more than 6 months after the initiation of treatment. (■), treated with systemic corticosteroid; (□), treated with supportive therapy alone; *, sclerodermoid graft-versus-host disease (GVHD)-like lesions.

drug.[45] The patient had low TSH and elevation of FT4 without symptoms of hyperthyroidism, and tests for anti-TSH receptor antibody and thyroid-stimulating immunoglobulin were negative at that time. Autoimmune thyroiditis can develop following the relapse of DIHS/DRESS.[46]

The emergence of Hashimoto's disease, characterized by the presence of anti-TPO antibody and anti-thyroglobulin antibodies, has also been observed after the resolution of DIHS/DRESS. The authors have encountered a patient with DIHS/DRESS who developed Hashimoto's disease 3 years after resolution of the clinical symptoms of DIHS/DRESS, characterized by elevated levels of anti-TPO and anti-thyroglobulin antibodies.[3] Alopecia has been noted in patients with autoimmune thyroid disease.[2,3,40] The presence of HHV-6 in the thyroid was significantly higher in Hashimoto's thyroiditis than in controls, highlighting a possible association between HHV-6 reactivation and autoimmune thyroid disease.[47,48]

Type 1 diabetes mellitus as a sequela in DIHS/DRESS

Some cases of fulminant type 1 diabetes mellitus (FT1D) have been associated with DIHS/DRESS.[49–52] FT1D is a subtype of type 1 diabetes mellitus (T1D) characterized by an abrupt onset, absence of islet-related autoantibodies, and nearly complete destruction of pancreatic β-cells. The initial symptoms of T1D are vomiting and dull epigastric pain; laboratory examinations reveal hyperglycemia, hyperosmolarity and metabolic acidosis, and a relatively normal glycosylated hemoglobin level; these features are compatible with diabetic ketoacidosis. The onset of FT1D is characterized by elevated levels of pancreatic exocrine enzymes such as lipase and amylase, which is consistent with acute pancreatitis.

According to a nationwide survey in Japan, there were 15 cases of FT1D associated with DIHS/DRESS between 1985 and 2010. The mean age at onset of FT1D associated with DIHS/DRESS was 53.4 years; the interval between the onset of DIHS/DRESS to the development of FT1D was 39.9 days (range, 13–199 days). The incidence of FT1D in patients with DIHS/DRESS (0.54%) is much higher than that in the general Japanese population (0.010%).[53] The clinical manifestations of FT1D associated with DIHS/DRESS are similar to those not associated with DIHS/DRESS. It is possible that genetic susceptibility contributes to the development of FT1D. Notably, the incidence of HLA-B62 is significantly increased in this type of diabetes mellitus in Japanese patients with DIHS/DRESS. Viral reactivation may contribute to the development of FT1D in patients with DIHS/DRESS, based on the observation that FT1D is associated with viral infections such as influenza B, HHV-6, herpes simplex virus, and Coxsackie B3 virus.[54,55] In this setting, the rapid and severe damage to pancreatic β-cells may be caused by viral infections, an immune response, or an interplay between viruses and the immune response.[56]

By contrast, autoimmune T1D is rare in patients with DIHS/DRESS. In autoimmune T1D, various autoantibodies including anti-glutamic acid decarboxylase (GAD) and islet cell antibodies are detected. The coexistence of autoimmune T1D and autoimmune thyroiditis has been associated with DIHS/DRESS.[45] In this case, various autoantibodies including insulinoma antigen 2 (IA2), anti-GAD, anti-TPO, anti-thyroglobulin, and anti-SSA antibodies and ANA were detected over a period of several months. A case of T1D following methimazole-induced hypersensitivity syndrome has been reported,[51] in which high glucose levels with a low serum C-peptide were detected 5 months after the onset of DIHS/DRESS in a patient with Graves' disease. Interestingly, anti-GAD antibodies were detected but at a relatively low level. A case of FT1D and Hashimoto's disease that developed concurrently after the onset of DIHS/DRESS has been reported, characterized by the presence of anti-thyroglobulin antibodies, ANA, and anti-SSA antibodies with an absence of GAD and islet cell antibodies.[57]

The consequences of missing the diagnosis of T1D can be fatal. It is essential to recognize the initial symptoms of T1D in patients with DIHS/DRESS in order to initiate appropriate treatment.

Other sequelae in DIHS/DRESS

Besides autoimmune thyroiditis and T1D, other autoimmune sequelae—heralded by autoimmune manifestations and/or presence of autoantibodies—can arise after resolution of DIHS/DRESS following a symptom-free interval of several months to years. These autoimmune diseases include sclerodermoid graft-versus-host disease (GVHD)-like lesions,[40] lupus erythematosus,[58] autoimmune hemolytic anemia (AIHA),[2] and rheumatoid arthritis (Table 2).

The authors have encountered three interesting cases of DIHS/DRESS with autoimmune sequelae of sclerodermoid GVHD-like lesions and autoimmune thyroiditis, atypical SLE, and rheumatoid arthritis, which appeared 3.5 years, 4 years, and 10 years after resolution of DIHS/DRESS, respectively. The first patient had a history of zonisamide-induced DIHS/DRESS and presented with fatigue and symptoms of thyroid dysfunction; diffuse alopecia on the scalp and multiple ill-defined brownish, indurated plaques with xerosis on the

Table 2 Autoimmune diseases as sequelae in DIHS/DRESS.

Alopecia
AIHA
Graves' disease
Hashimoto's disease
Lupus erythematosus
Rheumatoid arthritis
Sclerodermoid GVHD-like lesion
T1D (fulminant and autoimmune)

AIHA = autoimmune hemolytic anemia; DIHS/DRESS = drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms; GVHD = graft-versus-host disease; T1D = type 1 diabetes mellitus.

extremities were observed on examination.[40] Interestingly, ANA was negative during the course of DIHS/DRESS, but was detectable at the time of presentation to our hospital.[40] The second patient had a history of carbamazepine-induced DIHS/DRESS with reactivation of HHV-6 and EBV, and presented with a high-grade fever, general fatigue, cervical lymphadenopathy, and erythematous lesions on his face and ears.[58] After resolution of DIHS/DRESS, he developed prominent cervical lymphadenopathy. Histological findings of a lymph node biopsy specimen were compatible with those of Kikuchi-Fujimoto disease, and expression of EBV-encoded RNA (EBER) was detected in the lymph node by *in situ* hybridization, but not in the blood. Clinical manifestations of SLE including fever, general fatigue, discoid lesions, leucopenia, and proteinuria appeared 2 weeks after the onset of Kikuchi-Fujimoto disease. The third patient had a history of carbamazepine-induced DIHS/DRESS with the appearance of autoantibodies such as ANA, anti-TPO, and anti-thyroglobulin antibodies after the resolution of DIHS/DRESS. The autoantibody levels fluctuated without overt clinical symptoms. Ten years after the onset of DIHS/DRESS, the patient developed rheumatoid arthritis with characteristic joint deformities of the hands. It was noted that the second and third cases of DIHS/DRESS had been treated with supportive therapy alone. Chen et al described a case of AIHA and suspected SLE after the resolution of dapsone-induced DIHS/DRESS.[2] In that case, the patient had a high lactate dehydrogenase level, elevated percentage of reticulocytes, decreased haptoglobin concentration, and a positive Coombs test.

Pathomechanism of autoimmune disease in DIHS/DRESS

The pathomechanism underlying the emergence of autoimmune disease in DIHS/DRESS is poorly understood. A genetic susceptibility may contribute to their development.[53] Based on long-term follow-up of patients with DIHS/DRESS, several observations regarding the development of autoimmune sequelae were noted: young patients[2] and those treated with non-corticosteroid therapy were more susceptible,[3] and that herpesvirus reactivation—in particular, Epstein-Barr virus reactivation—is implicated in its development.[3,56]

From an immunological perspective, our previous study showed that the number of fully functional $CD4^+CD25^+FoxP3^+$ regulatory T (Treg) cells is markedly increased during the course of DIHS/DRESS compared with other drug reactions, which contributed to viral reactivation. These $FoxP3^+$ T cells lost their ability to inhibit the cytokine production and proliferation of effector T cells, which coincided with their contraction upon clinical resolution of DIHS/DRESS. The functional defect of Treg cells might be responsible for the development of autoimmune disease.[8,56,59]

Conclusion

In summary, the development of long-term sequelae after resolution of severe cutaneous adverse drug reactions may be overlooked because of an asymptomatic interval after resolution of the acute disease. The emergence of sequelae should be closely monitored following the resolution of SJS/TEN and DIHS/DRESS, especially autoimmune disease in DIHS/DRESS. The reactivation of herpesviruses and development of autoimmune disease in DIHS/DRESS may indicate a possible link between viral infections and autoimmune disease.

Acknowledgments

This work was supported by the "Research on Measures for Intractable Diseases" Project, and matching fund subsidies from the Ministry of Health, Labour, and Welfare, and the Ministry of Education, Culture, Sports, Science, and Technology of the Japanese Government. The authors thank Dr Chie Sotozono for his contribution on the description of ocular lesions.

References

1. Sotozono C, Ang LP, Koizumi N, Higashihara H, Ueta M, Inatomi T. New grading system for the evaluation of chronic ocular manifestations in patients with Stevens-Johnson syndrome. *Ophthalmology* 2007;**114**:1294–302.
2. Chen YC, Chang CY, Cho YT, Chiu HC, Chu CY. Long-term sequelae of drug reaction with eosinophilia and systemic symptoms: a retrospective cohort study from Taiwan. *J Am Acad Dermatol* 2013;**68**:459–65.
3. Ushigome Y, Kano Y, Ishida T, Hirahara K, Shiohara T. Short- and long term outcomes of 34 patients with drug-induced hypersensitivity syndrome in a single institution. *J Am Acad Dermatol* 2013;**68**:721–8.
4. Valeyrie-Allanore L, Bastuji-Garin S, Guégan S, et al. Prognostic value of histologic features of toxic epidermal necrolysis. *J Am Acad Dermatol* 2013;**68**:e29–35.
5. Sekula P, Dunant A, Mockenhaupt M, et al. Comprehensive survival analysis of a cohort of patients with Stevens-Johnson syndrome and toxic epidermal necrolysis. *J Invest Dermatol* 2013;**133**:1197–204.
6. Tohyama M, Watanabe H, Murakami S, et al. Possible involvement of CD14+ CD16+ monocyte lineage cells in the epidermal damage of Stevens-Johnson syndrome and toxic epidermal necrolysis. *Br J Dermatol* 2012;**166**:322–30.
7. Azukizawa H, Sano S, Kosaka H, Sumikawa Y, Itami S. Prevention of toxic epidermal necrolysis by regulatory T cells. *Eur J Immunol* 2005;**35**:1722–30.
8. Takahashi R, Kano Y, Yamazaki Y, Kimishima M, Mizukawa Y, Shiohara T. Defective regulatory T cells in patients with severe drug eruptions: timing of the dysfunction is associated with the pathological phenotype and outcome. *J Immunol* 2009;**182**:8071–9.
9. Viard I, Wehrli P, Bullani R, et al. Inhibition of toxic epidermal necrolysis by blocade of CD95 with human intravenous immunoglobulin. *Science* 1998;**282**:490–3.
10. Nassif A, Moslehi H, Le Gouvello S, et al. Evaluation of the potential role of cytokines in toxic epidermal necrolysis. *J Invest Dermatol* 2004;**123**:850–5.
11. Nomura Y, Aihara M, Matsukura S, et al. Evaluation of serum cytokine levels in toxic epidermal necrolysis and Stevens-Johnson syndrome compared with other delayed-type adverse drug reactions. *J Dermatol* 2011;**38**:1076–9.
12. Chung WH, Hung SI, Yang JY, et al. Granulysin is a key mediator for disseminated keratinocyte death in Stevens-Johnson syndrome and toxic epidermal necrolysis. *Nat Med* 2008;**14**:1343–50.
13. Lin A, Patel N, Yoo D, DeMartelaere S, Bouchard C. Management of ocular conditions in the burn unit: thermal and chemical burns and Stevens-Johnson syndrome/toxic epidermal necrolysis. *J Burn Care Res* 2011;**32**:547–60.
14. Kunimi Y, Hirata Y, Aihara M, Yamane Y, Ikezawa Z. Statistical analysis of Stevens-Johnson syndrome caused by mycoplasma pneumonia infection in Japan. *Allergol Int* 2011;**60**:525–32.
15. Meyer Sauteur PM, Goetschel P, Lautenschlager S. *Mycoplasma pneumoniae* and mucositis – part of the Stevens-Johnson syndrome spectrum. *J Dtsch Dermatol Ges* 2012;**10**:740–6.
16. Ueta M, Tokunaga K, Sotozono C, et al. HLA-A* 0206 with TLR3 polymorphisms exerts more than additive effects in Stevens-Johnson syndrome with severe ocular surface complications. *PLoS One* 2012;**7**:e43650.
17. Kaser DJ, Reichman DE, Laufer MR. Prevention of vulvovaginal sequelae in Stevens-Johnson syndrome and toxic epidermal necrolysis. *Rev Obstet Gynecol* 2011;**4**:81–5.
18. De Jesus LE, Dekermacher S, Manhães CR, Faria LM, Barros ML. Acquired labial sinechiae and hydrocolpos secondary to Stevens-Johnson syndrome. *Urology* 2012;**80**:919–21.
19. Sibaud V, Fricain JC, Lèautè-Labrèze C, Campana F, Taieb A. Persistant mucosal ulcerations: a rare complication of toxic epidermal necrolysis. *Ann Dermatol Venereol* 2005;**132**:682–5.
20. Kreft B, Lieser U, Haase R, Marsch WC, Wohlrab J. Extensive hypertrophic scarring after toxic epidermal necrolysis in a child. *Pediatr Dermatol* 2012. http://dx.doi.org/10.1111/j.1525-1470.2012.01863.x.

21. Sotozono C, Ueta M, Koizumi N, et al. Diagnosis and treatment of Stevens-Johnson syndrome and toxic epidermal necrolysis with ocular complications. *Ophthalmology* 2009;**116**:685–90.
22. Roujeau JC, Phlippoteau C, Koso M, Wechsler J, Andre C, Binaghi M. Sjögren-like syndrome after drug induced toxic epidermal necrolysis. *Lancet* 1985;**1**:609–11.
23. Akosa AB, Elhag AM. Toxic epidermal necrolysis a study of the sweat glands. *J Cutan Pathol* 1995;**22**:359–64.
24. Shoji T, Cockerell CL, Koff AB, Bhawan J. Eruptive melanocytic nevi after Stevens-Johnson syndrome. *J Am Acad Dermatol* 1997;**37**:337–9.
25. Moosbrugger EA, Adams BB. Disseminated eruptions of ectopic sebaceous glands following Stevens-Johnson syndrome. *J Am Acad Dermatol* 2011;**65**:446–8.
26. Woo T, Saito H, Yamakawa Y, Komatsu S, Onuma S, Okudela K. Severe obliterative bronchitis associated with Stevens-Johnson syndrome. *Intern Med* 2011;**50**:2823–7.
27. Kamada N, Kinoshita K, Togawa Y, Kobayashi T, Matsubara H, Kohno M. Chronic pulmonary complications associated with toxic epidermal necrolysis: report of a severe case with anti-Ro/SS-A and a review of the published work. *J Dermatol* 2006;**33**:616–22.
28. Tan YM, Goh K. Esophageal stricture as a late complication of Stevens-Johnson syndrome. *Gastrointest Endosc* 1999;**50**:566–8.
29. Misra SP, Dwivedi M, Misra V. Esophageal stricture as a late sequel of Stevens-Johnson syndrome in adults: incidental detection because of foreign body impaction. *Gastrointest Endosc* 2004;**59**:437–40.
30. Descamps V, Bouscarat F, Laglenne S, et al. Human herpesvirus 6 infection associated with anticonvulsant hypersensitivity syndrome and reactive haemophagocytic syndrome. *Br J Dermatol* 1997;**137**:605–8.
31. Suzuki Y, Inagi R, Aono T, Yamanishi K, Shiohara T. Human herpesvirus 6 infection as a risk factor for the development of severe drug-induced hypersensitivity syndrome. *Arch Dermatol* 1998;**134**:1108–12.
32. Tohyama M, Yahata Y, Yasukawa M, et al. Severe hypersensitivity syndrome due to sulfasalazine associated with reactivation of human herpesvirus 6. *Arch Dermatol* 1998;**134**:1113–7.
33. Hashimoto K, Yasukawa M, Tohyama M. Human herpesvirus 6 and drug allergy. *Curr Opin Allergy Clin Immunol* 2003;**3**:255–60.
34. Chiou CC, Yang LC, Hung SI, et al. Clinicopathological features and prognosis of drug rash with eosinophilia and systemic symptoms: a study of 30 cases in Taiwan. *J Eur Acad Dermatol Venereol* 2008;**22**:1044–9.
35. Kano Y, Ishida T, Hirahara K, Shiohara T. Visceral involvements and long-term sequelae in drug-induced hypersensitivity syndrome. *Med Clin North Am* 2010;**94**:743–59.
36. Chen YC, Chiu HC, Chu CY. Drug reaction with eosinophilia and systemic symptoms. A retrospective study of 60 cases. *Arch Dermatol* 2010;**146**:1373–9.
37. Wei CH, Chung-Yee Hui R, Chang CJ, et al. Identifying prognostic factors for drug rash with eosinophilia and systemic symptoms (DRESS). *Eur J Dermatol* 2011;**21**:930–7.
38. Cacoub P, Musette P, Descamps V, et al. The DRESS syndrome: a literature review. *Am J Med* 2011;**124**:588–97.
39. Wongkitisophon P, Chanprapaph K, Rattanakaemakorn P, Vachiramon V. Six-year retrospective review of drug reaction with eosinophilia and systemic symptoms. *Acta Derm Venereol* 2012;**92**:200–5.
40. Kano Y, Sakuma K, Shiohara T. Sclerodermoid graft-versus-host disease-like lesions occurring after drug-induced hypersensitivity syndrome. *Br J Dermatol* 2007;**156**:1061–3.
41. Shiohara T, Kano Y, Takahashi R, Ishida T, Mizukawa Y. Drug-induced hypersensitivity syndrome: recent advances in the diagnosis, pathogenesis and management. *Chem Immunol Allergy* 2012;**97**:122–38.
42. Ishida T, Inaoka M, Hirahara K, Kano Y, Shiohara T. Enhanced production of autoantibodies following resolution of drug-induced hypersensitivity syndrome. *Rinsyo Hifuka* 2010;**64**:260–4 in Japanese.
43. Cookson H, Creamer D, Walsh S. Thyroid dysfunction in drug reaction with eosinophilia and systemic symptoms (DRESS): an unusual manifestation of systemic drug hypersensitivity. *Br J Dermatol* 2013;**168**:1130–2.
44. Teo RY, Tay YK, Tan CH, Ng V, Oh DC. Presumed dapsone-induced drug hypersensitivity syndrome causing reversible hypersensitivity myocarditis and thyrotoxicosis. *Ann Acad Med Singap* 2006;**35**:833–6.
45. Brown RJ, Rother KI, Artman H, Mercurio MG, Wang R, Looney RJ. Minocycline-induced drug hypersensitivity syndrome followed by multiple autoimmune sequelae. *Arch Dermatol* 2009;**145**:63–6.
46. Funck-Brentano E, Duong T, Family D, et al. Auto-immune thyroiditis and drug reaction with eosinophilia and systemic symptoms (DRESS) associated with HHV-6 viral reactivation. *Ann Dermatol Venereol* 2011;**138**:580–5.
47. Descamps V. DRESS (drug reaction with eosinophilia and systemic symptoms) and thyroiditis: HHV-6, the possible common link. *Br J Dermatol* 2013. http://dx.doi.org/10.1111/bjd.12456.
48. Caselli E, Zatelli MC, Rizzo R, et al. Virological and immunological evidence supporting an association between HHV-6 and Hashimoto's thyroiditis. *PloS Pathog* 2012;**8**:e1002951.
49. Sekine N, Motokura T, Oki T, et al. Rapid loss of insulin secretion in a patient with fulminant type 1 diabetes mellitus and carbamazepine hypersensitivity syndrome. *JAMA* 2001;**285**:1153–4.
50. Sommers LM, Schoene RB. Allopurinol hypersensitivity syndrome associate with pancreatic exocrine abnormalities and new-onset diabetes mellitus. *Arch Intern Med* 2002;**162**:1190–2.
51. Ozaki N, Miura Y, Sakakibara A, Oiso Y. A case of hypersensitivity syndrome induced by methimazole for Graves' disease. *Thyroid* 2005;**15**:1333–6.
52. Chiou CC, Chung WH, Hung SI, Yang LC, Hong HS. Fulminant type 1 diabetes mellitus caused by drug hypersensitivity syndrome with human herpesvirus 6 infection. *J Am Acad Dermatol* 2006;**54**(Suppl. 2):S14–7.
53. Onuma H, Tohyama M, Imagawa A, et al. High frequency of HLA B62 in fulminant type 1 diabetes with the drug-induced hypersensitivity syndrome. *J Clin Endocrinol Metab* 2012;**97**:E2277–81.
54. Sano H, Terasaki J, Tsutsumi C, Imagawa A, Hanafusa T. A case of fulminant type 1 diabetes mellitus after influenza B infection. *Diabetes Res Clin Pract* 2008;**79**:e8–9.
55. Van der Welf N, Kroese FG, Rozing J, Hillebrands JL. Viral infections as potential triggers of type 1 diabetes. *Diabetes Metab Res Rev* 2007;**23**:169–83.
56. Shiohara T, Kano Y. A complex interaction between drug allergy and viral infection. *Clin Rev Allergy Immunol* 2007;**33**:124–33.
57. Minegaki Y, Higashida Y, Ogawa M, Miyachi Y, Fujii H, Kabashima K. Drug-induced hypersensitivity syndrome complicated with concurrent fulminant type1diabetes mellitus and Hashimoto's thyroiditis. *Int J Dermatol* 2013;**52**:355–7.
58. Aota N, Hirahara K, Kano Y, Fukuoka T, Yamada A, Shiohara T. Systemic lupus erythematosus presenting with Kikuchi-Fujimoto's disease as a long-term sequela of drug-induced hypersensitivity syndrome, a possible role of Epstein-Barr virus reactivation. *Dermatology* 2009;**218**:275–7.
59. Aota N, Shiohara T. Viral connection between drug rashes and autoimmune diseases: how autoimmune responses are generated after resolution of drug rashes. *Autoimmun Rev* 2009;**8**:488–94.