REVIEW ARTICLE

Long-term outcome of patients with severe cutaneous adverse reactions

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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 obliteratorive 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.

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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, 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. 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, regulatory T cell function, Fas/Fas ligand and perforin/granzyme B, pro-inflammatory cytokines, and granulysin produced by natural killer cells. 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, which include conjunctivitis and epithelial sloughing in mild cases, and pseudo-membranous and membranous conjunctivitis and corneal and/or conjunctival epithelial defects with severe pain and photophobia in severe cases. Inflammation of the ocular surface frequently persist
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). 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 sequel 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

**Mu cocutaneous 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 hydrometrocolpos 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 ophthalic involvement (Figure 2).21 It is well known that Sjögren-like syndrome frequently

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**Table 1 Sequelae in SJS/TEN.**

<table>
<thead>
<tr>
<th>Ocular lesion</th>
<th>Conjunctiva: conjunctival hyperemia, symblepharon formation</th>
<th>Conjunctiva: conjunctival hyperemia, symblepharon formation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cornea: superficial punctate keratinopathy, epithelial defect, loss of palisades of Vogt, conjunctivalization, neovascularization, opacification, keratinization</td>
<td>Conjunctiva: conjunctival hyperemia, symblepharon formation</td>
<td></td>
</tr>
<tr>
<td>Conjunctiva</td>
<td>Conjunctiva: conjunctival hyperemia, symblepharon formation</td>
<td></td>
</tr>
<tr>
<td>Eyelid: trichiasis, mucocutaneous junction involvement, meibomian gland involvement, lacrimal gland and duct involvements, punctal damage</td>
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<td></td>
</tr>
</tbody>
</table>

**Mu cutaneous lesion**

<table>
<thead>
<tr>
<th>Urogenital system</th>
<th>Vaginal obstruction/vaginal stenosis, vulvovaginal adenosis/endometriosis, urinary stream egress obstruction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Pigmentary change, dry skin (xeroderma), appearance of melanocytic nevi or ectopic sebaceous gland, nail deformity</td>
</tr>
</tbody>
</table>

**Esophageal lesion**

<table>
<thead>
<tr>
<th>Stricture formation</th>
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</table>

| SJS/TEN – Stevens-Johnson syndrome/toxic epidermal necrolysis. |

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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. Dry skin and heat intolerance are common complaints among survivors of SJS/TEN with involvement of the eccrine duct, although the sebaceous gland is usually normal.

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. In a separate case, widespread eruption of ectopic sebaceous glands occurred 4 months after an episode of SJS. Similar to the aforementioned case, cytokines and growth factors were thought to be responsible for the proliferation of residual sebaceous gland cells.

**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. According to one report, pulmonary sequelae tend to occur in relatively young patients. 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 sequelae is unclear because some reported cases show persistent respiratory symptoms from the onset of SJS/TEN.

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 sequelae 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. 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.

**Sequela 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). Various internal organs can be affected during the course of disease. Furthermore, the development of autoimmune diseases several months to years after clinical resolution of DIHS/DRESS have been reported. Several autoimmune diseases can develop sequentially in a single patient. The emergence of autoimmune disease might be overlooked unless dermatologists perform long-term follow-up of patients after their recovery from DIHS/DRESS.

**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. Renal insufficiency following acute interstitial nephritis at the acute stage of DIHS/DRESS could require a lifetime hemodialysis. 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. The proportion of DIHS/DRESS patients with autoantibodies is higher than that seen in SJS/TEN patients. The percentage of DIHS/DRESS patients with autoantibodies was higher in the group that received supportive treatment alone than those who received systemic corticosteroids. 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. 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. Thyrotoxicosis can be the initial presenting symptom of thyroid disease. Two patients diagnosed with Graves' disease with symptoms of hyperthyroidism and elevation in FT4 plus suppression of TSH have been reported—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. Brown et al described a patient with Graves' disease confirmed by thyroid tests that developed 5 months after withdrawal of the causative
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 consequence 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.

**Type 1 diabetes mellitus as a sequela in DIHS/DRESS**

Type 1 diabetes mellitus (T1D) can arise after resolution of DIHS/DRESS. 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 antiglutamic acid decarboxylase (GAD) and islet cell antibodies are detected. The coexistence of autoimmune T1D and autoimmune thyroiditis has been associated with DIHS/DRESS.55

**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 scleroderma graft-versus-host disease (GVHD)-like lesions,50 lupus erythematosus,53 autoimmune hemolytic anemia (AIHA),2 and rheumatoid arthritis (Table 2). The authors have encountered three interesting cases of DIHS/DRESS with autoimmune sequelae of scleroderma 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
extremities were observed on examination. Interestingly, ANA was negative during the course of DIHS/DRESS, but was detectable at the time of presentation to our hospital. 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. 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 autoantibodies 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. 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. Based on long-term follow-up of patients with DIHS/DRESS, several observations regarding the development of autoimmune sequelae were noted: young patients and those treated with non-corticosteroid therapy were more susceptible, and that herpesvirus reactivation—in particular, Epstein-Barr virus reactivation—is implicated in its development.

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.

**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.

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**References**


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**Table 2** Autoimmune diseases as sequelae in DIHS/DRESS.

<table>
<thead>
<tr>
<th>Autoimmune Disease</th>
<th>DIHS/DRESS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alopeica</td>
<td>Drug-induced hypersensitivity syndrome</td>
</tr>
<tr>
<td>AIHA</td>
<td>Drug reaction with eosinophilia and systemic symptoms;</td>
</tr>
<tr>
<td>Graves’ disease</td>
<td>HHV-6 and EBV, and presented with a high-grade fever, general fatigue,</td>
</tr>
<tr>
<td>Hashimoto’s disease</td>
<td>cervical lymphadenopathy, and erythematous lesions on his face and ears.</td>
</tr>
<tr>
<td>Lupus erythematosus</td>
<td>After resolution of DIHS/DRESS, he developed prominent cervical</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>lymphadenopathy. Histological findings of a lymph node biopsy specimen</td>
</tr>
<tr>
<td>Sclerodermoid GVHD-like</td>
<td>were compatible with those of Kikuchi-Fujimoto disease, and expression</td>
</tr>
<tr>
<td>lesion</td>
<td>of EBV-encoded RNA (EBER) was detected in the lymph node by in situ</td>
</tr>
<tr>
<td>T1D (fulminant and autoimmmune)</td>
<td>hybridization, but not in the blood.</td>
</tr>
</tbody>
</table>

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.


