CASE IN POINT

Prolonged Drug-Induced Hypersensitivity Syndrome/DRESS With Alopecia Areata and Autoimmune Thyroiditis

2LT Kathleen Krivda, USA[a]; LTC John Campagna, MD, USA[b]; MAJ Salvatore Mignano, DO, USA[c]; and COL Sunghun Cho, MD, USA[a]

Background: Drug-induced hypersensitivity syndrome (DIHS), also called drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, is a potentially fatal drug-induced hypersensitivity reaction that is characterized by a cutaneous eruption, multiorgan involvement, viral reactivation, and hematologic abnormalities.
Case Presentation: We present a case of lamotrigine-associated DIHS/DRESS complicated by an unusually prolonged course requiring oral corticosteroids and narrow-band ultraviolet B treatment and with development of extensive alopecia areata and autoimmune thyroiditis.
Conclusions: DIHS/DRESS is a severe cutaneous adverse reaction that may require prolonged treatment until symptoms resolve. Oral corticosteroids are the mainstay of treatment, but long-term use is associated with significant adverse effects. Alternative therapies, such as cyclosporine, look promising, but further studies are needed to determine safety profile and efficacy. DIHS/DRESS patients also should be educated and followed for potential autoimmune sequelae.

Author affiliations can be found at the end of this article.
Correspondence: Kathleen Krivda (kathleen.krivda@usuhs.edu)

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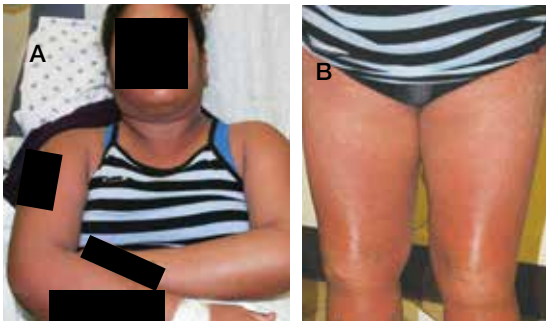
Drug-induced hypersensitivity syndrome (DIHS), also called drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, is a potentially fatal drug-induced hypersensitivity reaction that is characterized by a cutaneous eruption, multiorgan involvement, viral reactivation, and hematologic abnormalities. As the nomenclature of this disease advances, consensus groups have adopted DIHS/DRESS to underscore that both names refer to the same clinical phenomenon.[1] Autoimmune sequelae have been reported after DIHS/DRESS that include vitiligo, thyroid disease, and type 1 diabetes mellitus (T1DM). We present a case of lamotrigine-associated DIHS/DRESS complicated by an unusually prolonged course requiring oral corticosteroids and narrow-band ultraviolet B (UVB) treatment and with development of extensive alopecia areata and autoimmune thyroiditis.

CASE PRESENTATION

A 35-year-old female Filipino patient was prescribed lamotrigine 25 mg daily for bipolar II disorder and titrated to 100 mg twice daily after 1 month. One week after the increase, the patient developed a diffuse morbilliform rash covering their entire body along with facial swelling and generalized pruritus. Lamotrigine was discontinued after lamotrigine allergy was diagnosed. The patient improved following a 9-day oral prednisone taper and was placed on oxcarbazepine 300 mg twice daily to manage their bipolar disorder. One day after completing the taper, the patient presented again with worsening rash, swelling, and cervical lymphadenopathy. Oxcarbazepine was discontinued, and oral prednisone 60 mg was reinstituted for an additional 11 days.

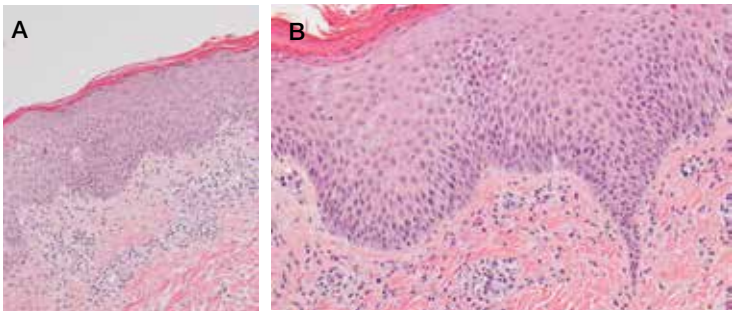
Dermatology evaluated the patient 10 days after completion of the second oral steroid taper (1 month after cessation of lamotrigine). The patient had erythroderma along with malaise, fevers, chills, and fatigue and a diffuse burning sensation (Figure 1). The patient was hypotensive and tachycardic with significant eosinophilia (42%; reference range, 0%-8%), transaminitis, and renal insufficiency. The patient was diagnosed with DIHS/DRESS based on their clinical presentation and calculated RegiSCAR score of 7 (score > 5 corresponds with definite DIHS/DRESS and points were given for fever, enlarged lymph nodes, eosinophilia ≥ 20%, skin rash extending > 50% of their body, edema and scaling, and 2 organs involved).[2] A punch biopsy was confirmatory (Figure 2A).[3] The patient was started on prednisone 80 mg once daily along with topical fluocinonide 0.05% ointment. However, the patient's clinical status deteriorated, requiring hospital admission for heart failure evaluation. The echocardiogram revealed hyperdynamic circulation but was otherwise unremarkable.

FIGURE 1 Acute Cutaneous Presentation of Drug Hypersensitivity



A, Significant facial swelling can be seen. B, Erythroderma with involvement of the trunk, upper and lower extremities can be seen.

FIGURE 2 Hemotoxin and Eosin Stain ×100 Magnification



A, Punch biopsy from the right wrist shows spongiosis and interface dermatitis with vacuolar changes. Necrotic keratinocytes in the epidermis, papillary dermal edema, and dermal eosinophils (center) can be seen. B, A second biopsy was performed 3 mo later, from the left arm, showing similar but less intense abnormalities to the previous biopsy.

The patient was maintained on prednisone 70 to 80 mg daily for 2 months before improvement of the rash and pruritus. The prednisone was slowly tapered over a 6-week period and then discontinued. Shortly after discontinuation, the patient redeveloped erythroderma. Skin biopsy and complete blood count (17.3% eosinophilia) confirmed the suspected DIHS/DRESS relapse (Figure 2B). In addition, the patient reported upper respiratory tract symptoms and concurrently tested positive for human herpesvirus 6 (HHV-6). The patient was restarted on prednisone and low-dose narrowband UVB (nbUVB) therapy was added. Over the following 2 months, they responded well to low-dose nbUVB therapy. By the end of nbUVB treatment, about 5 months after initial presentation, the patient's erythroderma improved, eosinophilia resolved, and they were able to tolerate prednisone taper. Ten months after cessation of lamotrigine, prednisone was finally discontinued. Two weeks later, the patient was screened for adrenal insufficiency (AI) given the prolonged steroid course. Their serum morning cortisol level was within normal limits.

Four months after DIHS/DRESS resolution and cessation of steroids, the patient noted significant patches of smooth alopecia on their posterior scalp and was diagnosed with alopecia areata. Treatment with intralesional triamcinolone over 2 months resulted in regrowth of hair (Figure 3). A month later, the patient reported increasing fatigue and anorexia. The patient was evaluated once more for AI, this time with low morning cortisol and low adrenocorticotrophic hormone (ACTH) levels—consistent with AI secondary to prolonged glucocorticoid therapy. The patient also was concomitantly evaluated for hypothyroidism with significantly elevated thyroperoxidase antibodies—confirming the diagnosis of Hashimoto thyroiditis.

FIGURE 3 Alopecia Areata on the Posterior Scalp

Regrowth of hair can be seen following intralesional triamcinolone injections.

DISCUSSION

DIHS/DRESS syndrome is a rare, but potentially life-threatening hypersensitivity to a medication, often beginning 2 to 6 weeks after exposure to the causative agent. The incidence of DIHS/DRESS in the general population is about 2 per 100,000.[3] Our patient presented with DIHS/DRESS 33 days after starting lamotrigine, which corresponds with the published mean onset of anticonvulsant-induced DIHS/DRESS (29.7-33.3 days).[4] Recent evidence shows that time from drug exposure to DIHS/DRESS symptoms may vary by drug class, with antibiotics implicated as precipitating DIHS/DRESS in < 15 days.[3] The diagnosis of DIHS/DRESS may be complicated for many reasons. The accompanying

TABLE RegiSCAR Scoring System for Drug-Induced Hypersensitivity Syndrome

	Score			
Criteria	**-1**	**0**	**1**	**2**
Fever ≥ 38.5 °C	No/unknown	Yes		
Enlarged lymph nodes		No/unknown	Yes	
Eosinophilia		No/unknown	≥ 0.7 x 10^9/L or ≥ 10% if WBC < 4.0 × 10^9/L	≥ 1.5 × 10^9/L or ≥ 20% if WBC < 4.0 × 10^9/L
Skin rash (> 50% body surface area)		No/unknown	Yes	
Skin rash[a]		No/unknown	Yes	
Skin biopsy suggesting DRESS	No	Yes/unknown		
Organ involvement		No	1 organ	≥ 2 organs
Rash resolution ≥ 15 d	No/unknown	Yes		
Excluding other causes[b]		No/unknown	Yes	

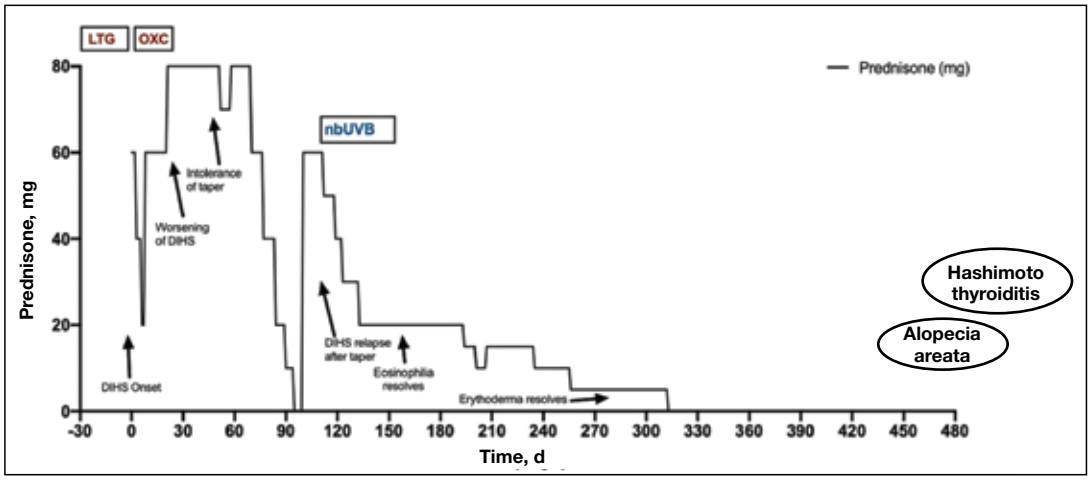
Abbreviations: DIHS, drug-induced hypersensitivity syndrome; DRESS, drug reaction with eosinophilia and systemic symptoms; WBC, white blood cell.
Diagnosis made based on total score: < 2 points: not DIHS; 2-3 points: possible DIHS; 4-5 points: probable DIHS; > 5 points: definitive case. Our patient received a score of 7, corresponding to a definite DIHS case.
[a]Suggests DRESS if ≥ 2 purpuric lesions, infiltration, facial edema, psoriasiform desquamation.
[b]If ≥ 3 negative: antinuclear antibody, blood culture, hepatitis A virus, hepatitis B virus, hepatitis C virus, chlamydia, mycoplasma.

rash may be morbilliform, erythroderma, or exfoliative dermatitis with multiple anatomic regions affected.[5] Systemic involvement with various internal organs occurs in > 90% of cases, with the liver and kidney involved most frequently.[5] Overall mortality rate may be as high as 10% most commonly due to acute liver failure.[5] Biopsy may be helpful in the diagnosis but is not always specific.[5] Diagnostic criteria include RegiSCAR and J-SCAR scores; our patient met criteria for both (Table).[5]

The pathogenesis of DIHS/DRESS remains unclear. Proposed mechanisms include genetic predisposition with human leukocyte antigen (HLA) haplotypes, autoimmune with a delayed cell-mediated immune response associated with herpesviruses, and abnormal enzymatic pathways that metabolize medications.[2] Although no HLA has been identified between lamotrigine and DIHS, HLA-A*02:07 and HLA-B*15:02 have been associated with lamotrigine-induced cutaneous drug reactions in patients of Thai ancestry.[6] Immunosuppression also is a risk factor, especially when accompanied by a primary or reactivated HHV-6 infection, as seen in our patient.[2] Additionally, HHV-6 infection may be a common link between DIHS/DRESS and autoimmune thyroiditis but is believed to involve elevated levels of interferon-γ-induced protein-10 (IP-10) that may lead to excessive recruitment of cytotoxic T cells into target tissues.[7] Elevated levels of IP-10 are seen in many autoimmune conditions, such as autoimmune thyroiditis, Sjögren syndrome, and Graves disease.[8]

DIHS/DRESS syndrome has been associated with development of autoimmune diseases as long-term sequelae. The most commonly affected organs are the thyroid and pancreas; approximately 4.8% of patients develop autoimmune thyroiditis and 3.5% develop fulminant T1DM.[9] The time from onset of DIHS/DRESS to development of autoimmune thyroiditis can range from 2 months to 2 years, whereas the range from DIHS/DRESS onset to fulminant T1DM is about 40 days.[9] Alopecia had been reported in 1, occurring 4 months after DIHS/DRESS onset. Our patient's alopecia areata and Hashimoto thyroiditis occurred 14 and 15 months after DIHS/DRESS presentation, respectively.

FIGURE 4 Interventions and Clinical Course



Abbreviations: DIHS, drug-induced hypersensitivity syndrome; LTG, lamotrigine; nbUVB, narrow-band ultraviolet light; OXC, oxcarbazepine.
LTG was started 33 d before presentation and OXC started at DIHS presentation, then discontinued shortly after. Treatment with nbUVB from d 90 to d 150. Arrows indicate clinical symptoms in relation to steroid course. Patient developed alopecia areata and Hashimoto thyroiditis 430 d and 460 d after DIHS onset, respectively.

Treatment

For management, early recognition and discontinuation of the offending agent is paramount. Systemic corticosteroids are the accepted treatment standard. Symptoms of DIHS/DRESS usually resolve between 3 and 18 weeks, with the mean resolution time at 7 weeks.[10] Our patient developed a prolonged course with persistent eosinophilia for 20 weeks and cutaneous symptoms for 32 weeks—requiring 40 weeks of oral prednisone. The most significant clinical improvement occurred during the 8-week period low-dose nbUVB was used (Figure 4). There also are reports outlining the successful use of intravenous immunoglobulin, cyclosporine, cyclophosphamide, rituximab, or plasma exchange in cases refractory to oral corticosteroids.[11]

A recent retrospective case control study showed that treatment of DIHS/DRESS with cyclosporine in patients who had a contraindication to steroids resulted in faster resolution of symptoms, shorter treatment durations, and shorter hospitalizations than did those treated with corticosteroids.[12] However, the data are limited by a significantly smaller number of patients treated with cyclosporine than steroids and the cyclosporine treatment group having milder cases of DIHS/DRESS.[12]

The risk of AI is increased for patients who have taken > 20 mg of prednisone daily ≥ 3 weeks, an evening dose ≥ 5 mg for a few weeks, or have a Cushingoid appearance.[13] Patients may not regain full adrenal function for 12 to 18 months.[14] Our patient had a normal basal serum cortisol level 2 weeks after prednisone cessation and then presented 5 months later with AI. While the reason for this period of normality is unclear, it may partly be due to the variable length of hypothalamic-pituitary-adrenal axis recovery time. Thus, ACTH stimulation tests in addition to serum cortisol may be done in patients with suspected AI for higher diagnostic certainty.[10]

CONCLUSIONS

DIHS/DRESS is a severe cutaneous adverse reaction that may require a prolonged treatment course until symptom resolution (40 weeks of oral prednisone in our patient). Oral corticosteroids are the mainstay of treatment, but long-term use is associated with significant adverse effects, such as AI in our patient. Alternative therapies, such as cyclosporine, look promising, but further studies are needed to determine safety profile and efficacy.[12] Additionally, patients with DIHS/DRESS should be educated and followed for potential autoimmune sequelae; in our patient alopecia areata and autoimmune thyroiditis were late sequelae, occurring 14 and 15 months, respectively, after onset of DIHS/DRESS.

Author affiliations
[a]Uniformed Services University of the Health Sciences, Bethesda, Maryland
[b]1st Theater Sustainment Command, Fort Knox, Kentucky
[c]Tripler Army Medical Center, Honolulu, Hawaii

Author disclosures
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Ethics and consent
The authors obtained written informed consent from the patient.

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