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LETTER

Alopecia universalis following DRESS, where rarities merge

Dear Sir,

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a severe, delayed-type drug hypersensitivity reaction that is characterized by fever, rash, lymphadenopathy, haematologic abnormalities (atypical lymphocytes, eosinophilia) and multi-organ involvement. Several autoimmune conditions that occur following DRESS have been reported previously. Here we present a woman who developed alopecia universalis (AU), 2 months after resolution of DRESS.

A 37-year-old woman admitted to emergency room reporting 2 weeks of a rash. She had a history of arthralgia and was prescribed salicylazosulfapyridine, paracetamol and dexketoprofen 1 month ago. On physical examination, confluent violescent erythematous patches

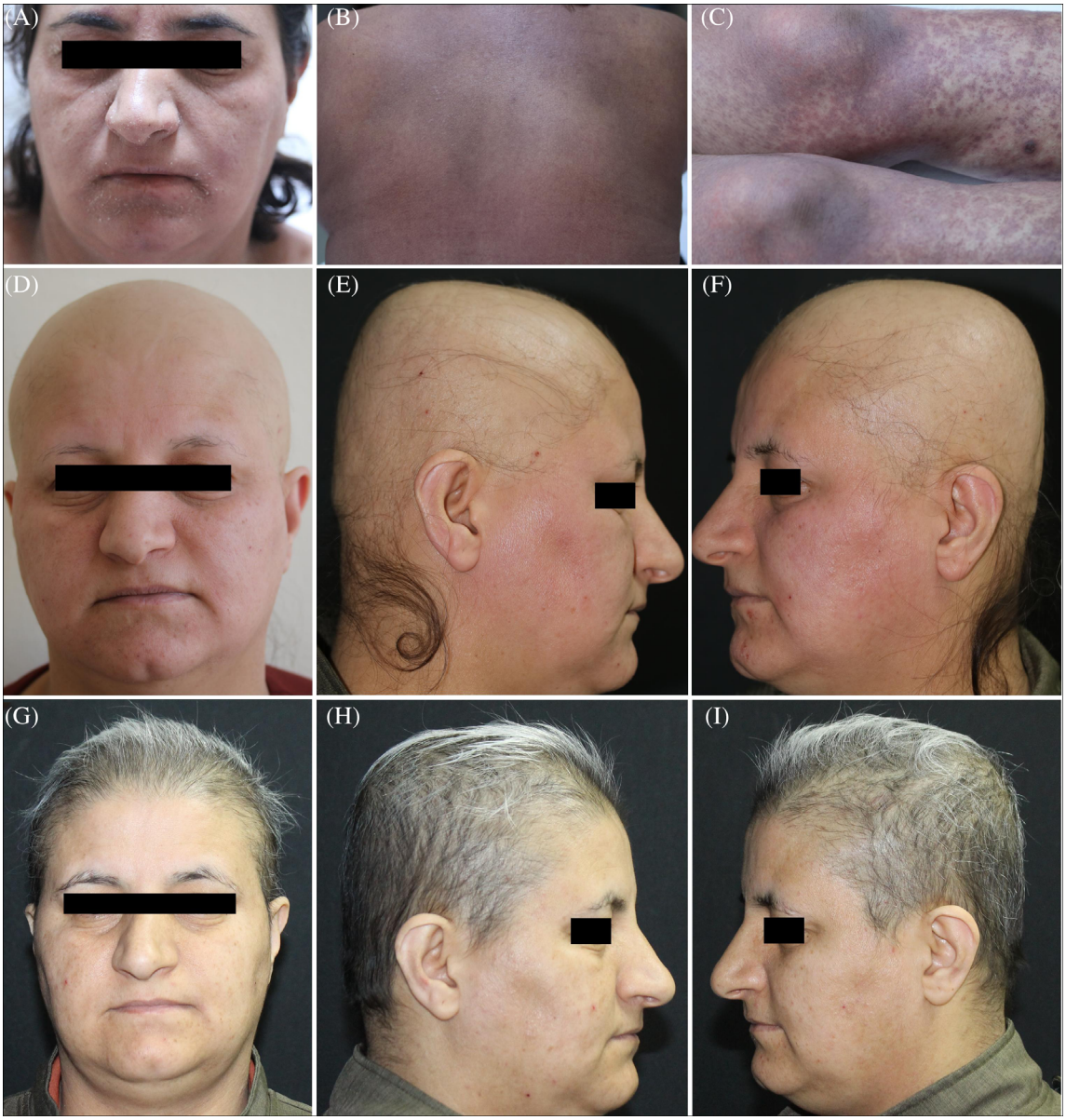

FIGURE 1 Facial edema and confluent livid patches at the initial presentation (A-C), alopecia areata in the third month of follow up (D-F) and recovery from alopecia after 6 months of the treatment (G-I)

TABLE 1 Previous six cases of alopecia areata (universalis) following DRESS

Previous six cases of alopecia areata (universalis) following DRESS			
Author	**Culprit drug**	**Time to development of alopecia**	**Autoimmune complication**
Huang et al[5]	Phenobarbital	3 months	Alopecia universalis
Chen et al[3]	Ampicillin	2 months after the onset of DRESS	Alopecia areata and Graves disease
Morita et al[6]	Trimethoprim-sulfamethoxazole	7 months	Alopecia totalis as a component of type III autoimmune polyglandular syndrome
Morita et al[6]	Zonisamide	5 months	Alopecia, vitiligo, type 1 diabetes, autoimmune thyroiditis
Lian et al[4]	Sulfasalazine	8 months	Alopecia universalis and vitiligo
Hollingsworth et al[7]	Lamotrigine	5 months	Alopecia universalis
This case Aksoy et al (2020)	Salicylazosulfapyridine	3 months	Alopecia universalis

on the trunk and extremities, fever, facial edema and bilateral axillary lympadenopathy were observed (Figure 1A-C). Laboratory examination revealed hypereosinophilia (3850/mm^3, 15.1%) and elevated liver enzymes (AST 53 U/L, normal <31 U/L; ALT 56 U/L, normal <37 U/L; LDH 797 U/L, normal: 135-214 U/L; γ-GT 60 U/L, normal <36 U/L). Histologically, spongiosis and basal vacuolar changes in the epidermis, and perivascular lymphocytic infiltration in the superficial dermis were demonstrated. The diagnosis of DRESS was made according to the European registry of severe cutaneous adverse reaction (RegiSCAR) scoring system.[1] The patient had already discontinued the potential culprit, salicylazosulfapyridine. Oral methylprednisolone 80 mg/d was initiated.

By the remission of the rash and facial edema, methylprednisolone was tapered and finally discontinued after 2 months. In the third month of follow-up, the patient developed diffuse non-scarring alopecia affecting the scalp, thereafter eyebrows and all of the body hair. She was diagnosed with alopecia universalis (Figure 1D-F). Laboratory studies that were performed to investigate any other autoimmune/endocrinological complications revealed low serum TSH levels. Thyroid hormones, anti-thyroglobulin, anti-thyroid peroxidase, plasma glucose, hemoglobin A1c, insulin, anti-insulin antibody, ACTH, and cortisol levels were normal and ANA, anti-ds DNA, anti-SSA, anti-SSB, anti-cardiolipin IgM, anti-cardiolipin IgG, anti-centromere, anti-GAD antibody, anti-Sm, anti-Sm/RNP, anti-Jo-1, anti-Scl-70, anti-mitochondrial antibody, anti-endomysium antibody, anti-gliadin IgA and anti-gliadin IgG were negative.

Intravenous pulse methylprednisolone (1 g/d, consecutive 3 days, monthly, 6 courses), oral methotrexate (15 mg/week), and, to eyebrows, intralesional triamcinolone acetonide (2.5 mg/mL, monthly, 2 courses) were administered to treat AU. Hair re-growth started in the eyebrows after 3 months, and was achieved in the entire body after 6 months of treatment (Figure 1G-I). No side effects were seen.

DRESS is a rare drug-induced reaction, manifests with a spectrum of systemic manifestations, characteristically present 2-6 weeks after initiation of the culprit drug. Common causative drugs include aromatic anticonvulsants, sulfonamides, and allopurinol. Susceptible HLA antigens and reactivation of herpesvirus have been proposed as pathogenetic mechanisms of DRESS. Diagnostic criteria of RegiSCAR include fever (≥38.5°C), lymphadenomegaly, eosinophilia, atypical lymphocytes, cutaneous involvement suggesting DRESS, organ involvement, duration (≥15 days), and absence of other potential causes of these findings.[1] Systemic corticosteroids, the gold standard treatment, need to be administered for 3-6 months and the dose should be tapered gradually to prevent the relapse.[2] The other treatment options for refractory cases are cyclosporine, intravenous immunoglobulin (IVIg), plasmapheresis, cyclophosphamide, and rituximab.

DRESS has been associated with the development of long-term autoimmune complications including alopecia areata, vitiligo, autoimmune thyroid diseases, type 1 diabetes, autoimmune hemolytic anemia, and autoimmune polyglandular syndrome.[3-5] Herpesvirus reactivation and regulatory T cell dysfunction during the resolution stage have been suggested to play a role in the development of autoimmune disorders following DRESS. To our knowledge, this is the seventh report of alopecia areata (universalis) as a sequela of DRESS (Table 1). Although we have discontinued methylprednisolone after 2 months, systemic corticosteroid therapy should be maintained for 3-6 months not to confront with relapse or autoimmune complications. Patients with DRESS should be followed-up closely in terms of long-term autoimmune consequences even after clinical and laboratory findings have improved.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

AUTHOR CONTRIBUTIONS

Hasan Aksoy, **Yasin Kucuk**, **Asli Turgut Erdemir**, **Ayse Serap Karadag**, **Mehmet Gurel**: Acquisition of data. **Hasan Aksoy**, **Ayse Serap Karadag**: Analysis and/or interpretation of data.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

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