Minocycline induced drug rash with eosinophilia and systemic symptoms complicated by hemophagocytic lymphohistiocytosis

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INTRODUCTION

Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome, also known as drug-induced hypersensitivity syndrome, is a severe, potentially life-threatening, complex hypersensitivity reaction occurring typically 1-6 weeks after exposure to certain medications or their metabolites. Estimates of overall population risk are between 1 in 1000 to 1 in 10,000 drug exposures.[1] It is classically associated with minocycline, aromatic anticonvulsants—phenytoin, carbamazepine, and phenobarbital — and sulfonamides — dapsone, sulfasalazine, and trimethoprim-sulfamethoxazole.[1] Hemophagocytic lymphohistiocytosis (HLH) is a rare, life-threatening syndrome characterized by fever, hepatosplenomegaly, cytopenias, coagulopathy, and elevated inflammatory markers among other findings.[2] It is distinguished as primary or secondary HLH depending on if the syndrome is driven through genotypic defects or through acquired/environmental mechanisms such as malignancy, infection, or medications.[2] Herein, we present a pediatric case of fatal minocycline-induced DRESS syndrome complicated by secondary HLH and multi-organ failure and discuss how the patient's case can inform future management.

Abbreviations used:

DRESS:	drug rash with eosinophilia and systemic symptoms
HLH:	hemophagocytic lymphohistiocytosis
IL:	interleukin

CASE REPORT

A 14-year-old female with a medical history of obesity was diagnosed with confluent and reticulated papillomatosis (CARP) and treated with minocycline 100 mg daily as an outpatient. Four weeks later, she was admitted to our intensive care unit after transfer from a local hospital with acute multiorgan dysfunction, acute kidney injury, hepatic dysfunction, pneumonia, shock, fever, lymphadenopathy, and facial edema. These symptoms first appeared after her second week of therapy and rapidly worsened. On week 3, she was admitted to a local hospital, minocycline was discontinued, and broad-spectrum antibiotics were administered. Her condition continued to deteriorate, and she was transferred to our academic center.

Physical exam showed a diffuse exanthematous eruption on the trunk; pseudovesicular erythematous papules on the face, chest, and intertriginous areas; and significant facial edema. There were hyperpigmented, reticulated plaques on the chest, with background Fitzpatrick skin type V-VI. Laboratory evaluation revealed multiple derangements including white blood cell 65.0 with eosinophil differential of 17%, creatinine 1.85, aspartate aminotransferase 2650, alanine transaminase 767, alkaline Phosphatase 181, prothrombin time 25.1, partial thromboplastin time 62.1, ferritin 9259.2, lactate dehydrogenase 7326, procalcitonin 82.18, fibrin 90, erythrocyte sedimentation rate 26.

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Multiple cytokines were elevated including interleukin (IL)-2, IL-2R, IL-4, IL-5, IL-6, IL-8, IL-10, IL-13, and IL-17, IFN-γ.

Multiple medical subspecialty teams were consulted. Extensive infectious disease workup for bacterial, viral, fungal, and tick-borne diseases was notable only for elevated human herpesvirus 6 polymerase chain reaction. Hematology oncology ruled out occult malignancy with flow cytometry, bone marrow biopsy, and comprehensive head and body imaging. Rheumatology evaluated autoimmune and autoinflammatory etiologies, including lupus, macrophage activation syndrome, and IgG4 related disease among others. Genetics performed whole genome sequencing, which eventually returned negative for all tested conditions. Human leukocyte antigen testing did not reveal any variants associated with DRESS.

The patient was diagnosed with minocycline-induced DRESS triggering a secondary HLH. Registry of Severe Cutaneous Adverse Reaction (RegiSCAR) score was calculated to be 7 (lymphadenopathy +1, atypical lymphocytes +1, peripheral eosinophilia >20% + 2, cutaneous eruption suggestive of DRESS +1, 2 or more internal organs involved +2). With the consideration of addressing both her DRESS syndrome and HLH, she was treated with aggressive immunosuppression on the second day of admission with high dose steroids (1gm methylprednisolone daily for 3 days, later dexamethasone 5 mg/m^2 daily), IL-1 blockade (anakinra), and IL-6 blockade (siltuximab). Janus kinase-signal transducer and activator of transcription (JAK-STAT) blockade (ruxolitinib) was added on the fourth day of admission. Total plasma exchange was performed on the third and fourth days of admission. Due to concern for possible infectious etiologies causing her sepsis-like symptoms, broad spectrum antibiotics were initially given and then later discontinued once her infectious workup returned largely negative. Despite these therapies, she continued to worsen and subsequently passed away due to recalcitrant hypotension and asystole.

DISCUSSION

Minocycline is a generally well-tolerated tetracycline antibiotic with uses in acne vulgaris, perioral dermatitis, and various inflammatory diseases such as rheumatoid arthritis, sarcoidosis, and confluent and reticulated papillomatosis.[3] In addition to our case, there have been several published cases of minocycline-induced DRESS resulting in death. Minocycline-induced DRESS commonly has multiorgan involvement of the liver (95% of patients), kidney (67% of patients), lung (43% of patients), myocardium (19% of patients), and endocrine system (19% of patients).[4] Although co-diagnosis of HLH and DRESS has been previously reported, there has been only 1 case of minocycline-induced HLH and DRESS to the best of our knowledge.[5,6] Notably, this case was similarly in a pediatric African American patient. HLH is a rare, frequently life-threatening, hyperinflammatory syndrome that frequently presents in the setting of genetic, rheumatologic, and malignant disease.[2] Most commonly, it is diagnosed when at least 5 out of the 8 diagnostic criteria are met: (1) fever, (2) splenomegaly, (3) cytopenia, (4) hypertriglyceridemia, (5) high ferritin, (6) hemophagocytosis, (7) decreased natural killer cell activity, or high CD25/IL-2.[2,5] Our patient demonstrated 7 out of the 8 criteria with exception of decreased natural killer cell activity. The previously reported patient only demonstrated 4 criteria: (1) fever, (2) splenomegaly, (3) high ferritin, and (4) hypertriglyceridemia.[5] In contrast with our patient, this patient's triglycerides were measured after the initiation of corticosteroids, making the etiology less clear between iatrogenic versus HLH-related hypertriglyceridemia.[5] Therefore, it would be advisable in the future to collect lipid testing prior to corticosteroid treatment for DRESS syndrome to avoid this potentially confounding result.

Several potential prognostic and mechanistic factors have been identified. Minocycline-induced DRESS occurs most frequently in patients with Fitzpatrick skin phototypes V and VI, such as the patient here.[4] This may be in part due to the preferential accumulation of minocycline in skin with higher melanin, promoting melanin-minocycline complexes.[7] Genetic abnormalities in key metabolic pathways/enzymes, such as cytochrome P-450, epoxide hydroxylase, and N-acetylation can similarly lead to a buildup of toxic drug byproducts.[1] Specific human leukocyte antigen variants are separately associated with DRESS syndrome and HLH, but there have not been any genotypes identified connecting the 2 diseases.

This fatal case of concurrent DRESS syndrome and HLH highlights several treatment considerations for future patients. When treating patients with skin of color with minocycline, it has been proposed that a lower dosage should first be trialed for at least 28 days, which is the mean latency period of minocycline-induced DRESS.[4] When there is a choice between minocycline and other tetracyclines, the latter carry a lower risk of DRESS.[4,8] Minocycline should be discontinued immediately following the development of concerning symptoms to prevent additional drug accumulation. Taken together, these measures may help mitigate severe minocycline-induced complications.

Conflicts of interest

None disclosed.

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