

Sorafenib Toxicity Mimicking Drug Reaction With Eosinophilia and Systemic Symptoms (DRESS) Syndrome

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ABSTRACT

Sorafenib is an oral multikinase inhibitor approved by the United States Food and Drug Administration for the treatment of advanced hepatocellular and renal cell carcinoma. Cases of sorafenib-induced Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome have been reported in the literature. DRESS syndrome is a potentially fatal, drug-induced hypersensitivity reaction that occurs 2-8 weeks after drug exposure. DRESS syndrome presents with generalized morbilliform eruption, facial edema, eosinophilia, and end-organ damage. We present the first reported case of sorafenib toxicity mimicking DRESS syndrome in a patient with metastatic adrenocortical carcinoma presenting with fever, morbilliform rash, and transaminitis in the absence of eosinophilia three days following initiation of sorafenib therapy. It is critical that clinicians are equipped to accurately diagnose DRESS syndrome due to its high mortality rate and the morbidity associated with prolonged steroid therapy.

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INTRODUCTION

Sorafenib is an antineoplastic agent that acts through inhibition of C-RAF and B-RAF kinases, vascular endothelial growth factor (VEGF), and platelet-derived growth factor receptor (PDGF).[1] Sorafenib has been approved by the United States Food and Drug Administration for the treatment of unresectable hepatocellular carcinoma[1] and advanced renal cell carcinoma.[2] Reported dermatologic toxicities secondary to sorafenib include hand-foot skin reaction, morbilliform eruption, desquamation, alopecia, pruritus, and xerosis.[1,3]

Sorafenib-induced Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome has been reported in the literature.[4] DRESS syndrome is a life-threatening, drug-induced hypersensitivity reaction that typically appears 2-8 weeks after drug exposure.[5] The classic presentation consists of a generalized morbilliform eruption, facial edema, eosinophilia, and end-organ damage.[5] The liver is most commonly involved, although the kidneys, heart, lungs, thyroid, bone marrow, and brain may also be affected.[5] In this article, we describe a case of sorafenib toxicity mimicking DRESS syndrome in a patient with metastatic adrenocortical carcinoma.

CASE

A 45-year old Korean woman with metastatic adrenocortical carcinoma presented to the emergency department with an 11-day history of daily measured fevers, headache, and rash. Dermatology was consulted for evaluation of the rash. The patient had been prescribed sorafenib 400 mg twice daily off-label for her metastatic adrenocortical carcinoma. On the third day of taking sorafenib, the patient developed morbilliform rash. Over the subsequent 5 days, she experienced facial swelling and generalization of the rash from her face to her trunk and extremities. She also experienced daily non-bilious emesis and non-bloody diarrhea beginning on day 8 of taking sorafenib.

The patient was febrile to 39.4°C during the first 2 days of admission. She had pronounced facial swelling and coalescing erythematous macules and patches with purpuric centers involving 90% of body surface area (Figures 1 and 2). Nikolsky's sign and mucosal involvement were absent. Lab abnormalities included transaminitis [AST 142 U/L (reference 5-40 U/L), ALT 60 U/L (reference 5-40 U/L)] without eosinophilia or leukocytosis. Creatinine and urinalysis were normal. Viral serologies (CMV, EBV, HHV-6, HSV-1, and HSV-2) were negative. The calculated European Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) score[5] was 3, indicating possible DRESS syndrome. Human Leucocyte Antigen (HLA) typing revealed alleles HLA-A*11:01:01G/-A*74:01:01G, HLA-B*15:01/-B*15:03:01G, and HLA-C *01:02:01G/-C*02:10.

The differential diagnosis initially included sorafenib toxicity and sorafenib-induced DRESS syndrome. Sorafenib was discontinued, and the patient subsequently defervesced, liver enzymes normalized, and her morbilliform eruption and facial swelling resolved.

TABLE 1.

Comparison of Characteristics of Sorafenib Toxicity and DRESS Syndrome[1-6]

Characteristic	Sorafenib Toxicity	DRESS Syndrome
Morbilliform Rash	+	+
Facial Swelling	+	+
Fever	+	+
Malaise	+	+
Diarrhea	+	+
Emesis	+	+
Transaminitis	+	+
Leukopenia	+	+
Thrombocytopenia	+	+
Eosinophilia	-	+
Lymphadenopathy	-	+
Multi-organ Involvement	-	+[a]

(+ = Present, - = Absent)
[a]DRESS syndrome can involve the liver, skin, kidneys, lungs, heart, pancreas, gastrointestinal tract, thyroid, brain, muscle, peripheral nerves, and eyes.

FIGURE 1. Coalescing erythematous macules and patches with purpuric centers involving the entire trunk.

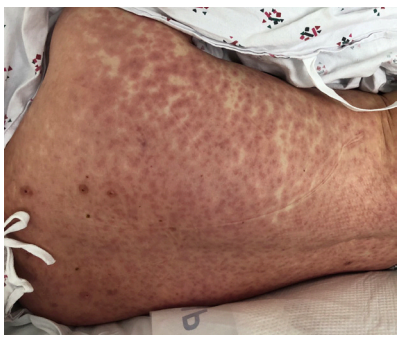
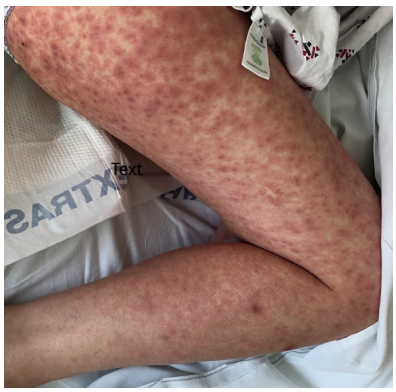


FIGURE 2. Extension of morbilliform eruption to lower extremity.



DISCUSSION

This is the first report in the literature of sorafenib toxicity mimicking DRESS syndrome. Due to the associated mortality[5] and frequent use of months-long steroid tapers for DRESS syndrome, it is important for clinicians to accurately diagnose DRESS. Similarly, it is crucial to distinguish sorafenib toxicity from DRESS syndrome to facilitate avoidance of high dose steroids when sorafenib toxicity is implicated in the setting of malignancy.

Several overlapping features have been reported for DRESS syndrome and sorafenib-induced toxicity (Table 1). Morbilliform rash, facial swelling, fever, malaise, and liver dysfunction are found in both sorafenib toxicity and DRESS syndrome. However, DRESS syndrome's hallmark features of eosinophilia, lymphadenopathy, and multi-organ involvement are absent in sorafenib toxicity. In the presented case, the onset of rash less than 2 weeks following sorafenib initiation and absence of eosinophilia, lymphadenopathy, or multi-organ involvement ultimately favored the diagnosis of sorafenib toxicity.

The overall incidence of rash and/or desquamation in sorafenib toxicity is estimated to be 35.4%.[6] Eruptions generally appear between 1-8 weeks after initiation of sorafenib.[6]The mechanism by which sorafenib induces morbilliform rash is not clear. It has been postulated that sorafenib causes temporary activation of the inflammatory cascade, with subsequent desensitization as the drug dose is altered.[3]This theory is supported by findings of rash resolution and ultimate tolerance documented in patients who continue sorafenib at lowered daily doses.[6] Further studies are warranted to elucidate this mechanism.

DISCLOSURES

None of the authors has conflicts of interest to disclose.

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