Enoxaparin-Induced DRESS Syndrome in a Pediatric Patient

Aarti Kamat[1], Mary McGrath[1], and Angela Weyand[1]

[1]University of Michigan Michigan Medicine

July 19, 2023

Abstract

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome is a drug hypersensitivity reaction characterized by rash, multiple systemic symptoms, and eosinophilia. DRESS syndrome develops following exposure to inciting medications, typically antibiotics and antiepileptics. Anticoagulants are not classically associated with this syndrome, though cases exist in association with vitamin K antagonists and oral anticoagulants. There are two known cases of enoxaparin-induced DRESS syndrome in adults, but no reports in the literature in the pediatric setting. In this report, we present the case of a pediatric patient who developed classic symptoms and lab findings of DRESS syndrome secondary to enoxaparin therapy.

Introduction

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome is a rare drug hypersensitivity reaction characterized by diffuse skin eruption and systemic symptoms including fever, lymphadenopathy, elevated transaminases, and eosinophilia.[1] DRESS syndrome typically develops 2-6 weeks after a viral infection or exposure to inciting medications, most commonly antibiotics, antiepileptics, and allopurinol.[1] The clinical presentation of DRESS syndrome is variable and non-specific, and is associated with high morbidity and mortality, therefore a high index of suspicion is necessary. While anticoagulants aren't typically associated with DRESS syndrome, there are documented cases in the literature involving vitamin K antagonists and oral anticoagulants, as well as two enoxaparin related cases in adult patients.[2,3,4] There are no reports of DRESS syndrome in children secondary to anticoagulants. We present a case of a pediatric patient with DRESS syndrome secondary to therapy. As anti-coagulants are increasingly prescribed to pediatric patients, especially in the wake of hyper-inflammatory syndromes caused be COVID19, it is crucial for pediatricians and pediatric hematologists to consider enoxaparin as a potential cause in patients with DRESS syndrome.

Case Presentation

A previously healthy 11-year-old female was admitted with sepsis secondary to osteomyelitis and a periosteal abscess of the left lower extremity, as well as methicillin-resistant staph aureus bacteremia. The patient was initiated on clindamycin and vancomycin for treatment of these infections. Ten days into her hospitalization, she was noted to have swelling of her left lower extremity and imaging revealed an acute deep venous thrombosis of the left popliteal vein. The patient was started on unfractionated heparin and subsequently transitioned to enoxaparin one week later.

Two weeks following enoxaparin initiation, the patient developed facial swelling, a generalized morbilliform rash over her face, trunk, and upper and lower extremities, and diffuse lymphadenopathy (palpable on physical examination and confirmed on radiologic imaging). She continued to have persistent, high-grade fevers despite multiple washouts of the extremity and appropriate antimicrobial coverage with negative blood cultures. Liver enzymes increased concurrently (AST 362 IU/L (normal 5-60 IU/L), ALT 371IU/L (normal <35 IU/L) at peak) with development of these symptoms. She had leukocytosis with atypical lymphocytes noted on peripheral smear. Eosinophilia was not present on her complete blood count (CBC) at the onset of these symptoms, though she did subsequently developed mild eosinophilia (1.1 K/ul at

peak). Human herpesvirus 6 (HHV6), cytomegalovirus (CMV), and Epstein Barr Virus (EBV) serologies were all negative. Skin biopsy was performed and was consistent with a drug eruption. With a score of 6, based on the RegiSCAR criteria, the patient's constellation of symptoms and biopsy findings were consistent with a definite case of DRESS syndrome. Given the diagnosis, treatment with high-dose steroids was initiated. Clindamycin and vancomycin were both discontinued due to their known association with DRESS syndrome, and she was transitioned to doxycycline. However, over the course of the next five days, no improvement in rash, fevers, or liver enzymes was seen. Enoxaparin, her only remaining medication, was therefore transitioned to apixaban. Within a few days, the patient improved with resolution of rash, fevers, and improvement of her laboratory abnormalities.

Discussion

The diagnosis of DRESS syndrome can be challenging due to its nonspecific presentation, particularly in pediatric patients where symptoms can overlap with common viral syndromes and Kawasaki disease. The first presenting symptoms typically involve fever and a maculopapular rash. Patients then develop lymphadenopathy and hematologic abnormalities, including leukocytosis with eosinophilia and atypical lymphocytes, as well as transaminitis.[5]Symptoms develop 2-6 weeks following exposure to an inciting drug and can also be triggered by viruses most commonly HHV6, as well as EBV and CMV.[1,5] The RegiSCAR is used to identify DRESS syndrome given the diagnostic uncertainty. The criteria includes a combination of symptoms (rash, fever, lymphadenopathy), laboratory findings (atypical lymphocytes, eosinophilia, elevated liver enzymes), biopsy results, duration of symptoms, and exclusion of other diagnosis (Table 1).[1,5] A score of 2-3 indicates possible, 4-5 indicates probable, and greater than 5 indicates a definite case of DRESS syndrome.[1,5]

If left untreated, given its multisystem involvement, DRESS syndrome can result in multi-organ failure and significant morbidity and mortality, with a 10% mortality rate.[1] A high index of suspicion is therefore required in order to prevent both short- and long-term complications, especially as immediate discontinuation of the offending medication is vital to control the disease.

The most common inciting drugs include antiepileptics (carbamazepine, phenytoin, phenobarbital), antibiotics (Bactrim, clindamycin, vancomycin), and allopurinol.[1,5] DRESS syndrome has been described rarely in association with Vitamin K antagonists and direct oral anticoagulants in adult patients.[2,3,4] In an in-depth examination of existing literature, there are only two reported cases of DRESS syndrome associated with enoxaparin therapy, both in adult patients, and no reports of pediatric DRESS syndrome secondary to anticoagulants. Rates of venous thromboembolism requiring treatment with anticoagulation have been increasing overall in the general pediatric population. This is especially true in the wake of the COVID-19 pandemic and increasing inflammatory syndromes in children post-infection. Enoxaparin is a widely used anticoagulant in the pediatric population. As such, general pediatricians, as well as specialists, should be comfortable with identifying and managing the complications associated with it. DRESS syndrome should be included on the differential for any patient on enoxaparin who develops rash, fevers, lymphadenopathy, and eosinophilia. Similarly, enoxaparin should be considered as a possible causative agent in patients diagnosed with DRESS syndrome.

References:

1. Brandon Pye, Jessica M. Aguilar, Ashley M. Maranich. A 15-year-old Boy Presents with Fever and Pruritic Rash for 6 Days. *Pediatrics in Review* January 2021; 42.
2. Dabas G, De D, Handa S, et al. Delayed-type hypersensitivity reaction to enoxaparin in a pregnant woman. *Postgrad Med J* 2019;95:506.
3. Ronceray S, Dinulescu M, Gall F, et al. Enoxaparin-Induced Dress Syndrome. *Case Rep Dermatol.* 2012 Sep-Dec; 4(3): 233–237.
4. Menteşoğlu D, Doğan Günaydın S, Ersoy-Evans S. Drug Reaction with Eosinophilia and Systemic Symptoms Syndrome Induced by Apixaban. *Dermatologic Therapy* . 2020; 33: e13719.
5. Cardones AR. Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome. *Clin Dermatol* . 2020;38(6):702-711.

Hosted file

Table 1.docx available at https://authorea.com/users/640016/articles/655498-enoxaparin-induced-dress-syndrome-in-a-pediatric-patient