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CLINICAL CASE REPORT

Minocycline-Induced Drug Reaction With Eosinophilia and Systemic Symptoms Syndrome

Myocarditis and Multiple Organ Failure

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Abstract: This article reports a case of minocycline-induced drug reaction with eosinophilia and systemic symptoms syndrome in a 16-year-old female who presented with acute myocarditis and severe heart failure. Drug reaction with eosinophilia and systemic symptoms syndrome is a severe, multisystem reaction. It is usually manifested by cutaneous, lymphatic, and solid organ involvement with progression to multisystem organ failure, following the use of several medications. There are 3 previous documented reports of drug reaction with eosinophilia and systemic symptoms syndrome–induced myocarditis. This is a case report and a review of the literature.

Keywords: drug reaction with eosinophilia and systemic symptoms, DRESS syndrome, eosinophilic myocarditis, heart failure, ventricular assist device, minocycline

Case Description

A 16-year-old, previously healthy female, was emergently transferred to our hospital, after presenting to her local emergency room in cardiogenic shock. Eight weeks prior to presentation, she initiated a course of minocycline for acne. Three weeks into her treatment, she developed a fever, malaise, fatigue, and posterior cervical lymphadenopathy as well as urticaria, a maculopapular rash, and significant edema of her face, limbs, and trunk. The patient was instructed to discontinue the antibiotic and start a course of oral prednisone. Initial laboratory evaluation showed an elevated white blood cell count of 25 000/μL, with 6% eosinophils and mildly elevated liver enzymes. Although a drug reaction was suspected, she was referred to an infectious disease specialist to rule out viral or bacterial etiologies.

Two weeks later, a repeat evaluation demonstrated a persistent leukocytosis with eosinophilia. An initial attempt to wean her steroids resulted in an exacerbation of her symptoms. During the second attempt to taper the steroids, the patient experienced a syncopal episode followed by intermittent chest pain, nausea, and orthopnea. She presented to her physician's office where an electrocardiogram was obtained and revealed a wide complex tachycardia (Figure 1). She was urgently referred to the emergency department where she was hypotensive with a heart rate of 220 beats per minute. A transthoracic echocardiogram was obtained reporting a left ventricular ejection fraction of 20% with severe global hypokinesis. She was urgently taken for angiography, during which time she developed respiratory distress, hypotension, and subsequent cardiac arrest. She was intubated and cardiopulmonary resuscitation was initiated. Once she regained a pulsatile organized cardiac rhythm, an Impella (Abiomed, Danvers, MA) left ventricular assist device was placed.

> "Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a severe, drug-induced reaction that affects multiple organ systems."

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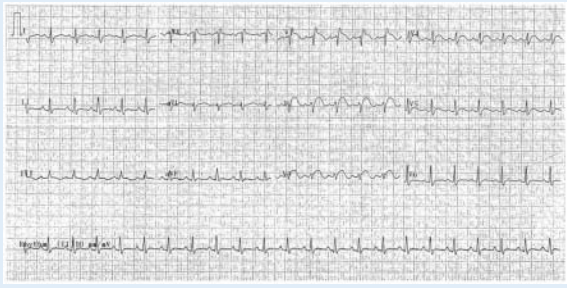

Figure 1. Patient's initial electrocardiogram performed at physician's office.

The patient was emergently transported to our facility for consideration for a ventricular assist device. On arrival she was unresponsive and mechanically ventilated. The Impella device was flowing approximately 1 L/min. On inotropic and vasopressor support she had a heart rate of 70 beats per minute and an undetectable blood pressure by palpation. Her initial transesophageal echocardiogram (TEE) in the operating room showed an ejection fraction of <8% with biventricular failure. The decision was made to proceed with extracorporeal membrane oxygenation and assess her neurological status. At this time, etiology of the patient's acute heart failure was unclear. She was started on broad spectrum antibiotics and was given high dose methylprednisilone and two days of immunoglobulin therapy. Viral and bacterial cultures were sent as well as autoimmune tests.

Postoperative day 1, she was in multiple system organ failure. Her liver function tests were extremely elevated (aspartate and alanine transaminases were greater than 5000 U/L, prothrombin time of 65 seconds, and international normalized ratio of 7.8). Continuous renal replacement therapy was initiated for acute renal failure. She was noted to have ischemic lower extremities and was taken back to the operating room for bilateral fasciotomies. On postoperative day 2, she was able to follow simple commands with her upper extremities. Over the following week, her clinical status improved. A repeat TEE revealed no ventricular recovery and a biventricular assist device (BiVAD) was implanted. A tissue sample was taken from the left ventricular apex and histopathologic examination demonstrated: myocarditis with lymphocytes, histiocytes, eosinophils as well as myofiber degeneration; some areas of necrosis; no viral, granulomatous, or vasculitis associated changes. Because of these pathologic findings and the fact that all other diagnostic tests were negative, her acute cardiomyopathy was thought to be due to eosinophilic myocarditis from minocycline exposure. She was given the diagnosis of drug reaction with eosinophilia and systemic symptoms syndrome (DRESS).

Her initial hospital course was complicated by hyperbilirubinemia, pancreatitis, ventilatory failure necessitating a tracheostomy, and septic shock. Her nutrition was maintained with postpyloric elemental feeds. Two weeks after BiVAD implantation, a TEE revealed improved biventricular recovery. The BiVAD was weaned and removed. With the assistance of high-dose inotropic support and inhaled nitric oxide, her left ventricular function was calculated to be 40% to 45% with moderately reduced right ventricular function. Her cardiac function worsened during attempts to wean her steroids, making high-dose methylprednisilone necessary. Eventually, her inotropic support was no longer required.

Two weeks after BiVAD explant, the patient developed an inability to tolerate enteral nutrition. Total parenteral nutrition was initiated. A colonoscopy showed dusky, friable, and thin mucosa. She urgently underwent a subtotal colectomy with ileostomy and pancreatic debridement secondary to noninfectious necrosis of her pancreatic tail. Gross dissection of her colon showed ischemic colitis. Although imaging was negative for splanchnic perfusion defects, her small bowel continued to appear ischemic, resulting in a persistent source of infection. Recurrent sepsis, high-dose steroids, and chronic total parenteral nutrition lead to an immunocompromised state. Although her left and right ventricular function appeared to have fully recovered, she developed multiple episodes of hypotension secondary to bacteremia and fungemia that required intermittent vasopressor agents.

Over the following 6 weeks, she was persistently catabolic, causing her wounds from multiple surgical sites, including her sternotomy, to dehisce. Her mental status waxed and waned. The patient required intermittent dialysis. Although she had been weaned from the ventilator, on hospital day 93, she developed a right main pulmonary embolus and was placed back on mechanical ventilatory support. She continued to deteriorate with recurrent acute hepatic failure, intra-abdominal hemorrhage, and severe intractable abdominal pain. A discussion with her parents resulted in the transition from curative to palliative efforts. Three days later, on hospital day 102, she expired.

Discussion

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a severe, drug-induced reaction that affects multiple organ systems. DRESS syndrome (the term coined by Helene Bocquet, Martine Bagot, and Jean Claude Roujeau in 1996) is characterized by fever, cutaneous manifestations of progressive severity, and lymphadenopathy. Hematologic abnormalities include eosinophilia and atypical lymphocytosis. Systemic involvement such as hepatitis, myocarditis, renal failure, or enteritis is paramount to the diagnosis.[1] Saltzstein and Ackerman[2] first documented this constellation of symptoms associated with anti-convulsants in 1959. This syndrome may occur following the use of several medications.[1,3,4]

The onset of symptoms most frequently occurs within 2 months following drug exposure. Patients may frequently exhibit symptoms of fatigue and anorexia. The cutaneous manifestations start as an erythematous, morbilliform rash affecting the face, upper extremities, and torso. The rash may progress to indurated lesions associated with vesicle and blister

Table 1. Medications Associated With Drug Reaction With Eosinophilia and Systemic Symptoms Syndrome[a]

Drug	Clear Association	Likely/Possible Association	Total Cases
Abacavir		1	5
Allopurinol	4	14	19
Augmentin		1	1
Amitriptyline		2	2
Atorvastatin		1	1
Aspirin	1		1
Captopril		1	1
Carbamazepine	14	30	47
Cefadroxil		1	1
Celecoxib		1	1
Chlorambucil		1	1
Clomipramine		1	1
Codeine phosphate		1	1
Cotrimoxazole/cefixime		1	1
Cyanamide		1	1
Dapsone		4	4
Diaphenylsulfone		1	1
Efalizumab		1	1
Esomeprazole		1	1
Hydroxychloroquine	2		2
Ibuprofen		2	2
Imatinib		1	1
Lamotrigine	2	5	10
Mexilletine		5	5
Minocycline	1	2	3
Nevirapine	2	6	8
Olanzapine	1		1
Oxcarbazepine	2	1	3
Phenobarbital	3	7	10
Phenylbutazone	1		1

(continued)

Table 1. (continued)

Drug	Clear Association	Likely/Possible Association	Total Cases
Phenytoin		6	7
Quinine and thiamine		1	1
Salazosulfapyridine	1	1	2
Sodium meglumine ioxitalamate		1	1
Sodium valproate/ethosiximide	1		1
Spirinolactone	1		1
Streptomycin	1		1
Strontium ranelate	1	1	2
Sulfalazine	5	5	10
Sulfamethoxazole		2	2
Tribenoside	1		1
Vancomycin	1	3	4
Zonisamide	1		1

[a]Adapted from Cacoub et al.[4]

formation and is accompanied by generalized, tender lymphadenopathy. Histologic examination of lymph nodes may show benign lymphoid hyperplasia or a pseudolymphoma pattern with destruction of normal histology by necrosis and edema, as well as atypical lymphocytic, histiocytic, and eosinophilic infiltration. Multisystem organ failure associated with this syndrome is often secondary to the eosinophilic infiltration and necrosis of native cellular components. The liver is documented as the most frequently affected solid organ. Patients present with hepatomegaly and/or hepatitis.[1]

Myocarditis in this syndrome is rare, with only 3 documented cases due to minocycline in the literature.[5-7] Myocarditis may present as chest pain, orthopnea, or syncope. Abnormalities include tachycardia, conduction defects, cardiomegaly, and/or biventricular failure.[8] The mechanism of myocardial damage is thought to be a delayed-type hypersensitivity reaction due to drug haptens binding to myocardial collagen fibrils.[9] Because the characteristic pathologic findings occur focally, they may be missed on biopsy.[7,10] Eosinophilic myocarditis unrelated to DRESS syndrome may have a history involving a malignancy, recent vaccination history (hepatitis B or meningococcus) or vasculitis.[11,12] Lung, kidney, and bowel inflammation may progress to failure. Long term sequelae include autoimmune thyroiditis and diabetes.[13]

DRESS syndrome is challenging to diagnose and the incidence, difficult to determine. It has been estimated to occur in 1/1000 to 1/10 000 anticonvulsant drug exposures.[14] Recently, Cacoub et al[4] extensively analyzed 172 reported cases of DRESS syndrome. This review showed that the mean age was 40 years, with a 53% male predominance. Ninety-seven percent of the cases were associated with skin rash, 88% with internal organ involvement (liver being the most common), 66% with hypereosinophilia, 64% with fever, and 56% with lymphadenopathy.[4] Minocycline is widely prescribed for the treatment of acne vulgaris because of its antimicrobial and anti-inflammatory properties. Between 1998 and 2003, the Food and Drug Administration reported that the adverse event rate for minocycline was 72 adverse events per 1 000 000 prescriptions.[5] A French-based study reported 18 cases of minocycline-induced DRESS syndrome from 1985 to 2000.[15]

Cacoub et al[4] identified 43 drugs as possible causes of DRESS syndrome (Table 1). Four cases involved minocycline.[5,11,16,17] There is a possible association with human herpesvirus-6 (HHV).[18-21] Descamps et al[22] tested viral serology in 7 patients with DRESS syndrome. All seven patients were positive for HHV-6. It is therefore postulated that an active infection with HHV-6 can cause/induce an exaggerated hypersensitivity reaction during drug exposure.[22] Other viruses that have been

implicated in the development of DRESS syndrome include human immunodeficiency virus, cytomegalovirus, Epstein–Barr virus and, HHV-7.[23-25]

Immediate withdrawal of the offending agent is the first step in treatment. Following this, there is no scientifically proven therapy for DRESS. A prolonged course of high-dose steroids has anecdotally been shown to improve symptoms associated with DRESS syndrome.[4,5,7] Other interventions that have had little to no efficacy in the treatment of DRESS syndrome include cyclosporine, OKT3, and mycophenolate. Rituximab and plasmapheresis showed improvement of left ventricular function in one case report.[5] If not diagnosed and treated in a timely manner, DRESS syndrome has life threatening consequences. Though her cardiomyopathy resolved, through the support of external cardiac assist devices, our patient was unable to overcome the damage caused to her other vital organs by such prolonged ischemia.

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