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Brief Report

Myocarditis in drug rash with eosinophilia and systemic symptoms

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Abstract Drug rash with eosinophilia and systemic symptoms is a drug hypersensitivity reaction. Hepatitis and nephritis are the most common visceral manifestations. Myocarditis is important to recognise, given the high mortality rate. We describe a child with drug rash with eosinophilia and systemic symptoms and discuss the role of N-terminal pro-hormone of basic natriuretic peptide in early recognition of associated myocarditis.

Keywords: Drug-induced hypersensitivity syndrome; eosinophilic myocarditis; N-terminal pro-hormone of basic natriuretic peptide; drug rash with eosinophilia and systemic symptoms; drug-induced hypersensitivity syndrome

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Case presentation

A 2-year-old girl presented with 2 weeks of fever and 1 week of progressive rash. Symptoms started 1 month after she was started on phenobarbital. On examination, temperature was 39.5°C (103.1°F), pulse 150 beats/minute, blood pressure 95/51 mmHg, respiratory rate 32 breaths/minute, and oxygen saturation of 98%. She was alert and in discomfort. Facial oedema, bilateral cervical adenopathy, and a desquamating erythematous rash were noted on the face, trunk, and extremities. Mucosal surfaces were erythematous with superficial erosions.

Laboratory values included white blood cell count 25,000/μl (30% neutrophils, 50% lymphocytes, 5% monocytes, 14% eosinophils, and 1% metamyelocytes), haemoglobin 10.5 g/dl, platelet count 239,000/μl, sodium 132 mmol/L, potassium 3.8 mmol/L, chloride 101 mmol/L, bicarbonate 19 mmol/L, blood urea nitrogen 3 mg/dl, creatinine 0.4 mg/dl, glucose 97 mg/dl, aspartate aminotransferase 446 U/L, alanine aminotransferase 456 U/L, alkaline phosphatase 193 U/L, total bilirubin 0.6 mg/dl, albumin 2.4 g/dl, and high-sensitivity C-reactive protein 56.5 mg/dl. Urinalysis revealed 100 mg/dl protein and 11–30 white blood cells per high-power field.

The patient was initially treated with two doses of intravenous immunoglobulin at 2 g/kg for presumed Kawasaki disease. Upon transfer to our hospital, she was diagnosed with drug rash with eosinophilia and systemic symptoms, also known as drug-induced hypersensitivity syndrome. She was treated with methylprednisolone 0.5 mg/kg/dose every 6 hours. Skin biopsy showed lymphocytic interface dermatitis with parakeratosis.

A week into her hospitalisation, she developed acute-onset hypotension, lactic acidosis, and acute kidney injury. Chest radiograph showed an enlarged cardiac silhouette, pulmonary oedema, and pleural effusions (Fig 1). Low-voltage QRS complexes were seen on electrocardiogram (Fig 2). Owing to concern for myocarditis, N-terminal pro-hormone of basic natriuretic peptide was obtained and found to be 55,060 pg/nl (normal range 0–125). An echocardiogram revealed global hypokinesis, left ventricular dilation, mild mitral and tricuspid regurgitation, and decreased contractility consistent with the diagnosis of myocarditis.

Discussion

Drug rash with eosinophilia and systemic symptoms is drug hypersensitivity reaction that occurs 2–8 weeks

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after drug exposure.[1] Reactivation of human herpesvirus 6 appears to play a role in the pathogenesis.[2] Most cases are due to anti-epileptics, allopurinol, and sulphonamides.[1]

Although both drug reaction with eosinophilia and systemic symptoms, Steven Johnson syndrome, and toxic epidermal necrolysis all have systemic involvement, the mucocutaneous features and time course help differentiate the conditions. Steven Johnson syndrome and toxic epidermal necrolysis are associated with deeper skin involvement, and onset is typically 1–2 weeks from drug exposure. In contrast, drug reaction with eosinophilia and systemic symptoms has a morbilliform appearance with facial swelling, later onset, and a protracted course. In addition, visceral involvement is more common (91%) and mucosal involvement is rare in drug rash with eosinophilia and systemic symptoms. The liver (75%) and kidney (37%) are the most common organs involved.[1] Thyroiditis is also a well-recognised complication, often occurring 3 months or more after the onset of the disease. Myocarditis occurs in 13% of patients. Myocarditis has been described as late as 4 months after the diagnosis of drug rash with eosinophilia and systemic symptoms and may occur after the cutaneous findings have resolved.[3,4]

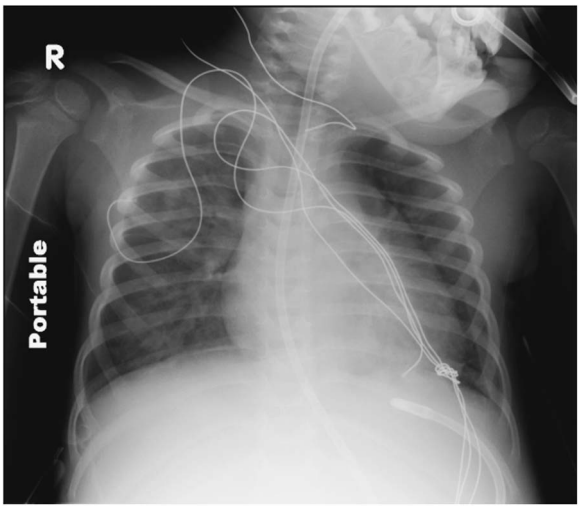

Figure 1.
Chest radiograph shows an enlarged cardiac silhouette, pulmonary interstitial oedema, and pleural effusions.

In a review of 22 patients with myocarditis associated with drug rash with eosinophilia and systemic symptoms, 12 patients died, 10 patients recovered, and 2 patients had residual cardiomyopathy. Several deaths occurred suddenly within hours of presentation: four patients died of a documented ventricular arrhythmia. Electrocardiogram changes include nonspecific ST and T-wave changes, conduction delay, and sinus tachycardia. Given the high mortality rates, cardiac screening with troponin, electrocardiogram, and echocardiogram has been recommended in

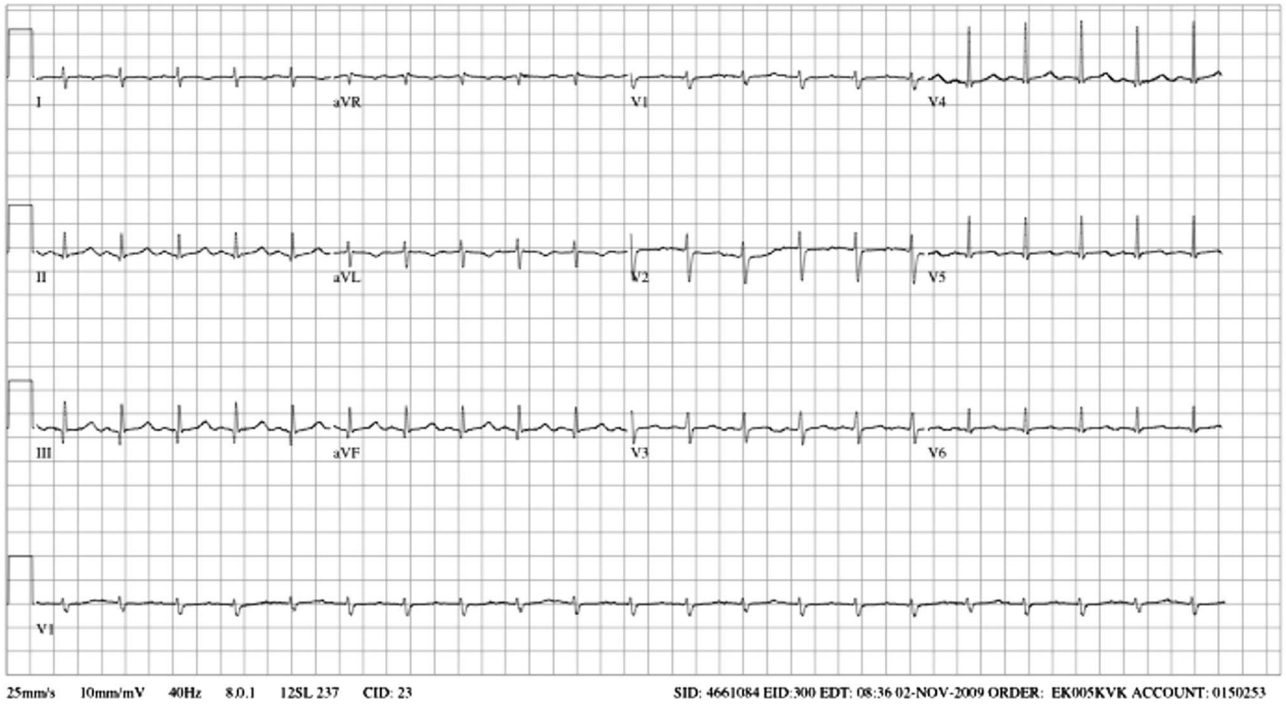

Figure 2.
EKG shows low-voltage QRS complexes consistent with the diagnosis of myocarditis. EKG = electrocardiogram.

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patients with drug rash with eosinophilia and systemic symptoms.[3]

Definitive diagnosis of myocarditis associated with drug rash with eosinophilia and systemic symptoms is made by endomyocardial biopsy. Histologic findings include a mixed eosinophilic and lymphocytic infiltrate. As the pattern of myocardial inflammation is patchy, sampling error may occur; therefore, biopsy should be reserved for patients with an unclear diagnosis or lack of response to corticosteroids and intravenous immunoglobulin.

We recommend obtaining N-terminal pro-hormone of basic natriuretic peptide levels in all patients with drug rash with eosinophilia and systemic symptoms. In our patient, obtaining N-terminal pro-hormone of basic natriuretic peptide may have allowed us to recognise myocarditis before her clinical decompensation. Values should be interpreted with caution as normal reference intervals vary by age, gender, puberty, and body habitus.[5]

N-terminal pro-hormone of basic natriuretic peptide may also play a role in assessing long-term morbidity. In one study (n = 23), elevated levels of N-terminal pro-hormone of basic natriuretic peptide were found to be associated with left ventricular dysfunction in children with myocarditis.[6] Conversely, normal values of N-terminal pro-hormone of basic natriuretic peptide are associated with echocardiographic recovery.[6] In another report of 10 patients with myocarditis, children with elevated N-terminal pro-hormone of basic natriuretic peptide 6 or 12 months after diagnosis were more likely to receive a cardiac transplant.[7]

Treatment of drug reaction with eosinophilia and systemic symptoms includes discontinuation of the offending agent, high-dose corticosteroids, and supportive care. Intravenous immunoglobulin is not routinely recommended;[8] however, for patients with myocarditis, intravenous immunoglobulin should be considered.[3,9] Relapse is common with tapering or discontinuation of steroids; therefore, steroids are continued for months to years before tapering.[10] Steroid-sparing immunosuppressive agents such as mycophenolate mofetil should be considered for patients with frequent relapses during steroid tapering.[3]

Our patient was initially treated with two doses of intravenous immunoglobulin (2 g/kg) by the transferring hospital followed by methylprednisolone 0.5 mg/kg/dose every 6 hours at our hospital. After 2 weeks, N-terminal pro-hormone of basic natriuretic peptide was 416 pg/ml and echocardiogram showed normal cardiac contractility. Serial measurements of N-terminal pro-hormone of basic natriuretic peptide were 55,060 pg/nl (initial), 15,763 pg/ml (4 days), 416 pg/ml (14 days), and 51 pg/ml (45 days). She was discharged after a 3-week hospitalisation with prednisone 2 mg/kg/day for 4 months followed by tapering. During her steroid tapering, she developed relapse of her rash and she was treated with high-dose intravenous methylprednisolone. After a duration of 7 months, she was again admitted for relapse after another attempted tapering and treated with intravenous immunoglobulin 2 g/kg and maintained on 0.5 mg/kg/day of prednisone. Echocardiogram showed normal cardiac function.

Myocarditis is a potentially fatal complication of drug reaction with eosinophilia and systemic symptoms. Early recognition and treatment with high-dose corticosteroids and intravenous immunoglobulin may improve clinical outcomes. As the time course of onset is variable and the clinical manifestations may be subtle, we recommend obtaining N-terminal pro-hormone of basic natriuretic peptide values in all patients with drug reaction with eosinophilia and systemic symptoms. We also recommend serial measurements for the first 6 months after diagnosis as myocarditis can present later in the disease course, after cutaneous manifestations have resolved.

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Conflicts of Interest

None.

References

1. Kardaun SH, Sekula P, Valeyrie-Allanore L, et al. Drug reaction with eosinophilia and systemic symptoms (DRESS): an original multisystem adverse drug reaction. Results from the prospective RegiSCAR study. Br J Dermatol 2013; 169: 1071–1080.
2. Shiohara T, Inaoka M, Kano Y. Drug-induced hypersensitivity syndrome (DIHS): a reaction induced by a complex interplay among herpesviruses and antiviral and antidrug immune responses. Allerg Int 2006; 55: 1–8.
3. Bourgeois GP, Cafardi JA, Groysman V, Hughey LC. A review of DRESS-associated myocarditis. J Am Acad Dermatol 2012; 66: e229–e236.
4. Bourgeois GP, Cafardi JA, Groysman V, et al. Fulminant myocarditis as a late sequelae of DRESS – 2 cases. J Am Acad Dermatol 2011; 65: 889–890.
5. Nir A, Lindinger A, Rauh M, et al. NT-Pro-B-type natriuretic peptide in infants and children: reference values based on combined data from four studies. Pediatr Cardiol 2009; 30: 3–8.
6. Nasser N, Perles Z, Rein AJ, Nir A. NT-proBNP as a marker for persistent cardiac disease in children with a history of dilated cardiomyopathy and myocarditis. Pediatr Cardiol 2006; 27: 87–90.

7. Mlczoch E, Darbandi-Mesri F, Luckner D, Salzer-Muhar U. NT-pro BNP in acute childhood myocarditis . J Pediatr 2012; 160: 178–179.
8. Joly P, Janela B, Tetart F, et al. Poor benefit/risk balance of intravenous immunoglobulins in DRESS. Arch Dermatol 2012; 148: 543–544.
9. Singer EM, Wanat KA, Rosenbach MA. A case of recalcitrant DRESS syndrome with multiple autoimmune sequelae treated with intravenous immunoglobulins. JAMA Dermatol 2013; 149: 494–495.
10. Chopra S, Levell NJ, Conley G, Gilkes JJ. Systemic corticosteroids in the phenytoin hypersensitivity syndrome. Br J Dermatol 1996; 134: 1109–1112.

https://doi.org/10.1017/S1047951114001735 Published online by Cambridge University Press