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DRESS Following FIRES: A Clinical Conundrum

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Abstract

A previously healthy 2-year old Hmong girl presented to the Emergency Department with first time seizures during a febrile illness. Seizures continued for the next two weeks despite multiple antiepileptic agents. All initial cultures and evaluations were negative, and febrile infection related epilepsy syndrome (FIRES) was diagnosed.

Three weeks into her hospital course, the patient developed a morbilliform rash on her thigh that became generalized. Concurrently, she developed fever and tachycardia. Laboratory studies demonstrated eosinophilia, an increase in ALT, AST, and direct/total bilirubin. CMV, EBV, and HHV-6 were negative. Skin biopsy showed lichenoid interface dermatitis. Clinical picture was suggestive of drug reaction with eosinophilia and systemic symptoms (DRESS). Topical and systemic steroids were started. Potential triggers for DRESS were discontinued. The patient deteriorated and cardiorespiratory failure occurred. She required ECMO for eight days. Patient gradually improved over the following weeks despite recurrent seizures and remained in the hospital for 283 days.

FIRES is a rare and highly morbid condition in which patients develop status epilepticus in the setting of febrile illness that is often intractable to anticonvulsants and steroids. Typically no causative infection is identified. DRESS, another rare and potentially fatal condition, is a drug hypersensitivity reaction that includes eosinophilia, characteristic skin findings and potential involvement of liver, lungs, kidneys, or other organs. Allopurinol, antiepileptic agents, and antibiotics are the most frequently reported triggers.

In this case report, we describe a patient who developed DRESS following FIRES, a sequence not previously described in the literature.

Keywords: Morbilliform; Drug reaction with eosinophilia and systemic symptoms; Recurrent seizures; Febrile infection related epilepsy syndrome

Abbreviations

DRESS: Drug Reaction with Eosinophilia and Systemic Symptoms; FIRES: Febrile Infection Related Epilepsy Syndrome; SLE: Systemic Lupus Erythematosus

Introduction

In this case report, we describe a patient who developed drug-related eosinophilia with systemic symptoms (DRESS) following febrile-illness related epilepsy syndrome (FIRES), a sequence not previously described in the literature. Below is a brief summary of the case including a review of both FIRES and DRESS.

Case Presentation

A previously healthy, developmentally appropriate, 2-year old Hmong girl presented to the Emergency Department (ED) with first time seizures presumed to be secondary to fever from an acute illness with otitis media. There was no prior history of seizures and there was no family history of seizures. On the day that she presented, a CT scan was completed and was concerning for mastoiditis but no intracranial pathology was noted. Broad coverage antibiotics were started secondary to the fever. Seizures continued in the ED, despite escalating anticonvulsant therapy. Desaturations occurred during the seizures and the patient required endotracheal intubation. Seizures continued for the next two weeks in the Pediatric Intensive Care Unit despite escalating antiepileptic use. Two days from presentation, a head MRI/MRV was obtained secondary to continued seizures that showed similar findings to the previous CT with findings only associated with the maxillary sinus and ethmoid air cells and no mention of mastoiditis. All initial cultures and evaluations returned negative and febrile infection related epilepsy syndrome (FIRES) was diagnosed. During her hospital course she received lorazepam, fosphenytoin, propofol, midazolam, fentanyl, phenobarbital, lacosamide, valproate, topiramate, felbamate, clonazepam, levetiracetam, and initiation of ketogenic diet to manage her seizures. High dose methylprednisolone and anakinra were given to treat potential neuroinflammation as an underlying cause.

The first seizure-free day was two weeks after presentation. At that time, her seizures were controlled with lacosamide, midazolam, phenobarbital, ketogenic diet, precedex, and anakinra. Eight days later, an insidious reticular rash started that evolved into a morbilliform rash on the patient's thigh and then generalized over the next two days to include her trunk, face, and extremities (Figure 1).

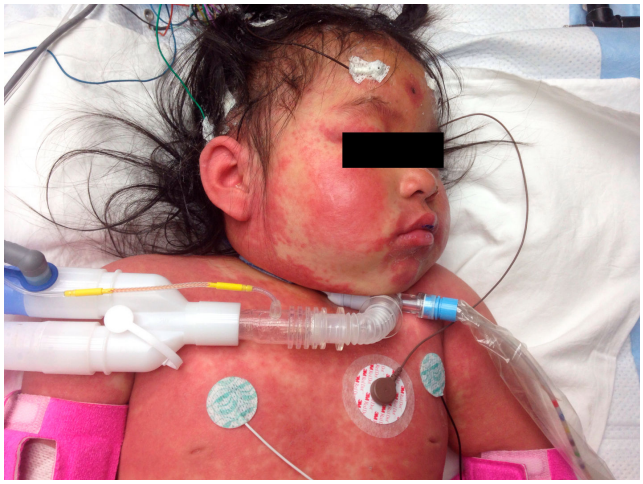

Figure 1: Rash during DRESS syndrome.

Mucous membranes were spared. Her symptoms did not improve with diphenhydramine. Concurrently, the patient developed fever and tachycardia. With the prolonged fever and rash findings, atypical Kawasaki's was investigated. An echocardiogram was obtained to rule out cardiac aneurysms associated with Kawasaki's disease and was found to be normal. Dermatology, Rheumatology, and Allergy were consulted. With the progression of these symptoms, laboratory studies were obtained and showed an eosinophilia, an increase in ALT, AST, and both direct and total bilirubin. CMV, EBV, and HHV-6 were negative. Skin biopsy was performed and showed lichenoid interface dermatitis. Because of the skin findings, time course, medication history, laboratory findings, and biopsy results, the patient was diagnosed with drug reaction with eosinophilia and systemic symptoms (DRESS). Topical and systemic steroids were initiated.

Phenobarbital, phenytoin, omeprazole, lacosamide, acetaminophen, ampicillin, cefotaxime, ceftriaxone, and vancomycin were discontinued and thought to be potential triggers for DRESS. The patient continued to clinically deteriorate in the three days following the appearance of the rash. Venous blood gas showed progressive respiratory acidosis. Echocardiogram showed failing ventricular function. Mechanical ventilation was required, and eventually vasoconstrictors and extracorporeal membrane oxygenation (ECMO) were started.

ECMO was continued for 8 days. The patient's clinical status improved over the following weeks with occasional recurrence of seizures. After failed extubation attempts, a tracheostomy was necessary for subglottic stenosis. Over the course of the illness, she developed significant oral aversion and initially received nutrition via nasogastric tube which was eventually changed to a gastrostomy tube.

Further evaluations over the course of the hospitalization included a Medical Genetics consult. A comprehensive (sequencing and deletion/duplication) analysis of epilepsy gene panel that look at 70 genes associated with epilepsy was obtained and no disease causing mutations were detected. Repeat head MRI was obtained 7 months after initial presentation that showed morphologically normal brain and no areas of hypo- or hyper- perfusion. A PET CT was obtained for prognostic value and this showed bilateral hypometabolism mainly involving her temporal lobes.

Patient remained in the hospital for 283 days, after which she was discharged home. At the time of discharge, her seizures were under control with anakinra, felbamate, levatiracetam, and clonazepam. It was believed that the use of anakinra was key in seizure control for this patient, suggesting a pathologic role for neuroinflammation. She was receiving half of her nutrition orally and the other half through her gastrostomy tube. She continued to work with PT and OT for deconditioning and to reach developmental milestones.

Almost three years after being discharged home, the patient is doing well. She was previously tracheostomy dependent and was decannulated one year after discharge from the hospital. She continues to have refractory epilepsy secondary to FIRES and mild global developmental delays particularly in her expressive language. Her seizures are well controlled with felbamate, levatiracetam, and as needed midazolam. She continues to progress in her oral intake and nutrition and is weaning from using her gastrostomy tube. She is enrolled in Head Start for ongoing therapies. Most recently, after developing multisystem involvement with leukopenia, low compliments, positive ds DNA, rash, and nephritis she was diagnosed with systemic lupus erythematosus (SLE). To the best of our knowledge, there is no association between FIRES or DRESS and SLE.

Discussion

Febrile infection–related epilepsy syndrome (FIRES) is a rare and highly morbid condition in which patients develop status epilepticus in the setting of febrile illness that is often intractable to anticonvulsants and steroids [1]. The estimated incidence is 1/1,000,000 [2]. It is the most severe and irreversible form of epilepsy. According to a review, there are clinical features associated with FIRES that consist of age of onset between 2-17 years, past medical history negative for seizures with normal psychomotor development, and negative family history [3]. It presents with explosive onset of multifocal or generalized seizures of different types evolving into refractory status epilepticus. EEG usually shows global slowing or multifocal discharges with bilateral frontotemporal predominance, or both. CSF is normal. MRI during the acute phase is normal, or it shows non-extensive bitemporal or diffuses abnormalities or has sporadic involvement of the basal ganglia or diffuse cortical edema. Work-up involving infectious, metabolic, and genetic investigations are usually without a causative finding.

A clear etiology has not been identified. It is presumed to be an immune-mediated epileptic encephalopathy that affects healthy children. No autoantibodies have been identified. One hypothesis is there is a release of inflammatory molecules following a systemic infection that activates the immune system involved in protecting the blood brain barrier which then gives rise to a neuroinflammatory cascade [4]. This neuroinflammation might lower seizure threshold rather than trigger the seizures.

In regard to treatment, systematic studies are lacking. Multiple case reports have stated that starting the patient on a ketogenic diet as soon as possible is the most effective treatment [5]. Anakinra is a recombinant version of the human interleukin-1 receptor antagonist used to treat auto-inflammatory disorders in neonates and children, and has shown powerful anticonvulsant properties in animal models [6].

MRI findings as described by Rivas-Coppola et al. showed evolution from normal imaging to severe cerebral atrophy. Progressive cytotoxic edema involving mostly bilateral hippocampi and temporal lobes were

noted after one to three weeks. Then within one month, mild-moderate cerebral atrophy and hippocampal sclerosis were noted and by one year severe cerebral and cerebellar atrophy was noted. Sequelae of FIRES are commonly drug-resistant epilepsy and neurologic and potentially psychologic impairments occurring without relief [7].

Drug reaction with eosinophilia and systemic symptoms (DRESS) is another rare and potentially fatal condition that includes eosinophilia, characteristic skin findings and potential involvement of lungs, liver, kidneys, or other organs. The frequency has been estimated to be 1 in 1000 to 1 in 10,000 drug exposures [5,6] A key feature is the delayed onset most often between 2 and 6 weeks after the drug was initiated. This helps to distinguish this drug reaction from others (i.e., SJS/TEN – 3 days to 3 weeks; acute generalized exanthematous pustulosis – 2 to 3 days) [8].

Clinical features of DRESS syndrome are fever, rash, eosinophilia, atypical lymphocytosis, and hepatitis. Facial edema is also a common feature of the disease [5]. Elevation of liver function tests occurs in a majority of the cases. Less commonly, kidneys, lungs, and heart are involved. High morbidity is associated with severe hepatitis in patients with DRESS [9]. Bocquet and colleagues developed three diagnostic criteria for DRESS syndrome which include:

- A skin eruption.
- Eosinophilia greater than 1500/uL.
- Internal organ involvement signified by transaminase elevation greater than 2 × normal, lymphadenopathy greater than 2 cm in diameter, or nephritis, interstitial pneumonia, or carditis [2].

Historically, histopathology findings have been described as non-specific in patients with DRESS syndrome. More recently, common histopathology findings identified include interface dermatitis, perivascular infiltration, and spongiosis [10-15].

DRESS syndrome falls into a type IV drug hypersensitivity reaction where there is T cell activation. It is believed that the characteristic clinical course of delayed onset, progressive course, and multi-organ injury is secondary to reactivation of viruses, specifically human herpesvirus-6 (HHV-6) but also EBV and CMV [6]. It is postulated that the combination of T cell activation and the viral activation cause the immune cascade of events.

As the name implies, DRESS syndrome is caused by a drug reaction. A 12 year review, done in 2012, of reported cases of DRESS found 44 suspected drugs [3]. The main drug categories involved are anticonvulsants, antibiotics, among others. Antiepileptic agents, specifically aromatic anticonvulsants, (e.g., carbamazepine, lamotrigine, phenytoin, phenobarbital) are the most frequently reported causes in children and in adults the most common cause is Allopurinol. Sulfonamides (particularly sulfasalazine), dapsone, and vancomycin may also induce DRESS. Treatment is aimed at withdrawal of the causative drug then interrupting the immune system by either corticosteroids or IVIg [6].

In this case report, we describe a patient who developed drug-related eosinophilia with systemic symptoms (DRESS) following febrile-illness related epilepsy syndrome (FIRES), a sequence not previously described in the literature.

Conclusion

A patient who developed drug-related eosinophilia with systemic symptoms (DRESS) following febrile-illness related epilepsy syndrome (FIRES), a sequence not previously described in the literature.

Acknowledgement

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Author's Contributions

Dahl, Knoebel, and Lloyd cared for the patient, conceptualized and designed the case report, drafted the initial manuscript, and reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Conflict of Interest

The authors have no conflicts of interest relevant to this article to disclose.

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