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CASE REPORT

Successful treatment of DRESS syndrome with plasmapheresis during the course of sero-negative autoimmune encephalitis: a case report

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ABSTRACT

Background: Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome manifests as a significant, medication-induced, adverse reaction with cutaneous, hematological and multi-organ involvement. Sero-negative autoimmune encephalitis is inflammation of the brain secondary to autoimmune processes in the absence of an identifiable autoantibody.

Case presentation: We present a pediatric case of sero-negative autoimmune encephalitis in which the patient subsequently developed DRESS syndrome as a result of exposure to ceftriaxone, omeprazole or acyclovir. She did not respond to either high-dose steroids or intravenous immunoglobulins (IVIG). Plasmapheresis was successful in treating symptoms relevant to both DRESS and sero-negative autoimmune encephalitis. No side effects were encountered.

Conclusion: To our knowledge, plasmapheresis has only been reported once to treat DRESS syndrome in a pediatric patient. Early recognition and treatment of this syndrome is paramount. We suggest that plasmapheresis is a relatively safe alternative treatment option for resistant cases especially within the context of other autoimmune conditions.

Keywords: Case Report, Plasmapheresis, DRESS syndrome, ceftriaxone, omeprazole, acyclovir, sero-negative autoimmune encephalitis.

Background

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a severe drug-hypersensitivity reaction that presents with an urticarial, maculopapular rash, hematological and multi-organ involvement (commonly deranged liver function). The symptoms range from a clinically mild presentation characterized by rash, transient eosinophilia and lymphadenopathy to a fulminating presentation with multiorgan failure. Treatment is with steroids; however optimum treatment for DRESS remains unclear and further data is needed [1].

Sero-negative autoimmune encephalitis is inflammation of the brain secondary to autoimmune processes and by definition there is no identifiable autoantibody [2]. Both the vague neuropsychiatric presentation and the lack of definitive tests, make the diagnosis of autoimmune encephalitis elusive. Delay in starting immunotherapy can lead to long-term neuropsychiatric sequelae [3]. First line treatments are immunosuppressive therapies such as high dose steroids and immunomodulatory therapies namely intravenous immunoglobulins (IVIG) and possibly

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plasmapheresis. Second line therapy may include rituximab, mycophenolate and cyclophosphamide. Literature is lacking with regard to indication, efficiency and side effects of plasmapheresis. There are neither randomized-controlled trials in pediatric patients nor direct comparison studies with other immunotherapies [4].

We herein describe a pediatric case with sero-negative autoimmune encephalitis, who developed DRESS syndrome and was successfully treated with plasmapheresis.

Case presentation

This, previously well, 15-year-old girl presented with altered behavior, agitation, visual and auditory hallucinations, headaches and insomnia for 3 weeks. Her speech was incoherent and inappropriate to situations. Prior to the onset of these symptoms, she had suffered from transient flu-like symptoms but had been taking no medication, including psychoactive drugs. She was a high achiever at school and a keen participant in sports. There were no relevant social, past medical or allergy histories. On examination, she was afebrile, disorientated and emotionally labile. She had expressive dysphasia and poor short-term memory with low scores on the 'Mini-mental state examination'. There were no focal neurological deficits and her systemic examination was unremarkable.

Electroencephalogram (EEG) had shown no specific abnormalities. Initial investigations were normal. These included inflammatory markers, extensive microbiological and virological studies, brain CT and MRI scans, wide metabolic and toxicological studies and screening for systemic autoimmune disorders and vasculitides. Furthermore, repeated testing both serologically and on the cerebrospinal fluid for antibodies associated with autoimmune encephalitis were negative. Those were: anti-NMDA receptors, anti-VGKC, anti-TPO, anti-GAD, anti-AMPA (1&2) receptors, anti-MOG and anti-GABA(B) receptor antibodies. Additionally, antineuronal antibodies were negative including Purkinji cell, neuronal nuclei, amphiphysin, anti CV2/CRMP-5, anti PNMA2 (Ma2/Ta) and anti-Tr antibodies. The paraneoplastic screen was also negative.

Initially, she was started on a course of intravenous ceftriaxone and acyclovir to treat possible infectious encephalitis pending confirmatory results. However, those were stopped after 5 days in light of the negative results. The potential diagnosis of 'autoimmune encephalitis' was then considered. Accordingly, she was commenced on intravenous methylprednisolone for 3 days followed by oral prednisolone at 40mg/kg/day with subsequent tapering for the following 6 weeks. She was also given omeprazole as a gastric-protecting agent.

She showed no improvement on the initial treatments as evidenced by serial neuropsychological assessments. She continued to exhibit abnormal behaviour, poor cognition and speech. Within 4 weeks from admission and whilst on tapering doses of prednisolone, a spreading purpuric maculopapular rash appeared as shown in figure 1. Her lips and tongue swelled and cracked. Several blood counts showed eosinophilia, which rose to a maximum of 10.4×10^9/L (range $0.0–0.8 \times 10^9$/L), and lymphopenia. She had a concomitant liver transaminitis but with preserved synthetic function. A whole-body MRI scan showed moderately enlarged inguinal, axillary and cervical lymph nodes groups. The diagnosis of DRESS syndrome was considered at this stage and omeprazole was stopped. A course of intravenous immunoglobulin (IVIG) at 2g/kg was given. However, neither her neuropsychiatric status nor had her DRESS syndrome symptomatology improved. A skin biopsy revealed inflammatory changes suggestive of an allergic reaction. An abdominal ultrasound showed evidence of gallbladder 'sludge' which improved subsequently. To rule out occult malignancy, she also had a bone marrow biopsy and aspirate, which revealed a normocellular marrow but with enhanced eosinophilia.

As her symptoms had not improved, plasmapheresis treatment was instituted via central venous access. In view of episodes of agitation, she was commenced on risperidone and was closely monitored throughout the plasmapheresis course in the ward. After 5 cycles, which expanded over 2 weeks, her rash began to disappear with a significant drop in the eosinophil count and liver transaminases. There were no side effects from this treatment. Alongside this, her behaviour improved dramatically which was mirrored by a boost in neurophysiological scores and a gradual return to her premorbid state. To consolidate this remission, she was subsequently treated with rituximab.

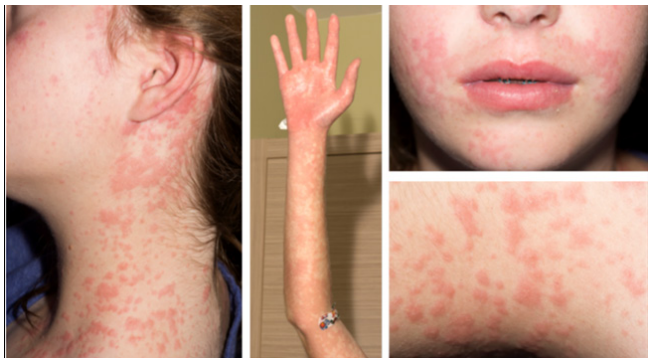

Figure 1: *Widespread florid maculopapular purpuric rash with swelling of the lips*

Table 1: *Diagnostic criteria for Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome. These criteria are an amalgamation of criteria established by a Japanese consensus group [6], an American group [7] and a British group published in the British Journal of Dermatology (2007) [8]. The only contentious features* are that of the reactivation of the HHV-6 and the leukocytosis. The diagnosis is made based on presence of three of the six remaining criteria.*

	Diagnostic Criteria for DRESS Syndrome	Case features	Criterion fulfilled?
1	Maculopapular rash developing > 3 weeks after starting with the suspected drug	*Present*	√
2	Prolonged clinical symptoms 2 weeks after discontinuation of the suspected drug	*Present*	√
3	Fever (> 38°C)	*Brief fever*	√
4	Involvement of a least one internal organ	*Present (hepatitis + enlarged spleen + gallbladder sludge)*	√
5	Leucocytosis (> 11 • 10⁹/L)/Atypical lymphocytosis (> 5%)*	*Leukocytosis*	√
6	Eosinophilia (> 1.5 • 10⁹/L)	*Highest eosinophils count 10.4 x 10⁹/L*	√
7	Lymphadenopathy at least two sites	*Present – confirmed by total body MRI*	√
8	Human herpesvirus 6 (HHV6) reactivation*	*HHV6 not detected*	×

Discussion

The diagnosis of DRESS syndrome is challenging due to its broad spectrum of clinical features and long latency. There is wide variation in outcome, ranging from mild to fatal. A mortality rate of 10% was quoted with most patients dying of liver failure [5]. Multiple sets of diagnostic criteria have been proposed but are hindered due to the considerable clinical heterogeneity in presentation. Our patient fulfilled the DRESS syndrome criteria as illustrated in table 1.

Other causes for the patient's symptoms should be considered before settling on the diagnosis of DRESS syndrome. Other systemic conditions with skin involvement were excluded including Kawasaki Disease (KD); an acute, self-limited vasculitis. The diagnosis of KD is clinical as the etiology is unknown currently and despite having lots of the overlapping features of KD, such as cervical lymphadenopathy and a rash, the diagnosis was excluded because she was afebrile and was too old. Other drug hypersensitivity reactions were considered such as Erythema multiforme (EM), Steven Johnson's Syndrome (SJS) and Toxic epidermal necrolysis (TEN). These life-threatening reactions were excluded mainly based on the excessively elevated eosinophils count on the blood, which was the cornerstone piece of evidence in her diagnosis. The rash did not show 'target lesions' (excluding EM) and did not peel (excluding SJS and TEN).

It is still unknown which drug triggered the patient's reaction. Over 50 drugs have been associated with DRESS syndrome; the most notorious among them are the anticonvulsants [1]. In the case described above, the possible culprits for triggering the DRESS syndrome were omeprazole, ceftriaxone or acyclovir. The specific hypersensitivity drug reaction seen in DRESS is rarely triggered by these medications as demonstrated by the few case reports [9,10]. We are unable to find a case report describing Acyclovir-induced DRESS syndrome, however there are documented cases of acyclovir triggering other hypersensitivity reactions [11,12]. Furthermore, these case reports are from the adult population; the literature is sparse regarding the incidence of DRESS syndrome in children. There are few studies that quote incidence at all, perhaps suggesting the rarity of the syndrome; however; estimates vary, with one paper suggesting an incidence of 0.4 per 1 million within the adult population [13]. Another paper quotes the estimated incidence to range from 1 in 1000 to 10,000 drug exposures [14].

The exact pathogenesis of DRESS syndrome remains unclear making targeted therapy futile. Suggested mechanisms for DRESS and other hypersensitivity syndromes include reactive metabolites leading to stimulation of CD4+ and CD8+ T cells through a variety of mechanisms, resulting in activation of eosinophils [1]. Efficient management of DRESS requires early recognition and withdrawal of offending medications. Currently, it is treated with high-dose oral corticosteroids, but response may be suboptimal and may lead to steroids overexposure. Other treatment options include immunosuppressive agents such as cyclosporine and cyclophosphamide, and IVIG. One intriguing aspect to this case is that she developed DRESS syndrome whilst on immunotherapy in the form of high dose steroids and IVIG. There have been reported cases of steroid-resistant DRESS syndrome but only one pediatric

case report of successfully treating DRESS syndrome using plasmapheresis [15]. It is thought that increased circulating cytokines contribute to the pathogenesis of DRESS and thus reducing circulating cytokine levels through plasmapheresis results in clinical improvement.

Concomitant occurrences of DRESS syndrome with other autoimmune disorders are frequently described in the literature. There have been multiple cases reported of DRESS syndrome leading to autoimmune hepatitis [16,17], autoimmune thyroid dysfunction [18,19], type 1 diabetes [20] and autoimmune limbic encephalitis [21]. The most common autoimmune sequelae are thought to be of thyroid dysfunction [22]. There are also reports on DRESS syndrome triggering cerebral vasculitis [23,24]. In a recent review by Y. Kano et al., it is suggested that regulatory T cells (Tregs) loss of function may be responsible for the association. Systemic corticosteroids administration may prevent the gradual loss of Treg function by repairing Treg activity [23]. Similarly, with plasmapheresis, the balance between Treg and other immunoactive cells is restored perhaps averting the pathology of the disease. It is important to note that an apparent link between the two disorders does not mean there is a causal relationship, hence the chronology of which came first, DRESS or the autoimmune disorder, should be highlighted. In the quoted cases above, the autoimmune disorders are seemingly triggered by the DRESS syndrome, however, in our case report the autoimmune encephalitis was observed prior to the onset of the DRESS syndrome. The association between DRESS and autoimmune disorders appears to be almost tangible. However, the etiology of DRESS must be delineated.

Plasmapheresis can be associated with risks such as central catheter dislodgment, sepsis and electrolyte disturbances however, this modality was safe in our patient. Close monitoring of the patient and pharmacological treatment of aggression made it possible to administer it on the ward. More importantly, it resulted in rapid resolution of both the neuropsychiatric symptoms and DRESS syndrome. Plasmapheresis has less toxicity than those encountered with many other immunomodulatory treatments.

Conclusion

There is currently no definitive treatment for DRESS syndrome and we suggest that plasmapheresis may have a larger role to play in its management. To our knowledge, this is the second pediatric DRESS syndrome case in which plasmapheresis was successful. We suggest that plasmapheresis is a relatively safe alternative treatment option for resistant cases especially within the context of other autoimmune conditions. Further research in this area is needed.

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List of Abbreviations

DM	Diabetes Mellitus
ICA	Islet Cell antibody
VPT	Vibration perception threshold

Conflict of Interests
None

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Consent for publication
Informed consent was obtained from the parents of the patient to publish this case in a medical journal.

Ethical approval
Ethical approval is not required at our institution for publishing a case report in a medical journal.

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Authors' contribution
MOEB conceived the idea, provided the framework and edited the manuscript. AT performed the extensive literature search and wrote the initial drafts. MLY provided the clinical data and also searched the literature. PS contributed to the clinical care of this case as did MOEB and MLY. All authors approved the final manuscript.

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Summary of the case

Patient (gender, age)	1	Female, 15 year old
Final Diagnosis	2	Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome secondary to treatment for seronegative autoimmune encephalitis
Symptoms	3	Altered behaviour, agitation, visual and auditory hallucinations, headaches and insomnia. She presented in a emotionally-labile state with expressive dysphasia and poor short memory
Medications (Generic)	4	Ceftriaxone, Aciclovir, Methylprednisolone (IV) for 3 days, Prednisolone (PO) at 40mg/kg/day, Omeprazole, Risperidone, Rituximab
Clinical Procedure	5	Plasmapheresis
Specialty	6	Paediatrics
Objective	7	To treat a challenging case
Background	8	Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a significant adverse-drug reaction, which can result in multi-organ failure. It is usually treated with high-dose steroids and other immunosuppressive medication.
Case Report	9	We describe a case, whereby the patient with DRESS syndrome was successfully treated with plasmapheresis.
Conclusions	10	There is currently no definitive management for DRESS syndrome and we suggest that plasmapheresis may have a larger role to play in its treatment.
MeSH Keywords	11	Case Report, Plasmapharesis, DRESS syndrome, ceftriaxone, omeprazole, aciclovir, sero-negative autoimmune encephalitis