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CASE REPORT

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Syndrome

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ABSTRACT

Introduction: DRESS (drug reaction with eosinophilia and systemic symptoms) syndrome is a potentially life-threatening illness with cutaneous and systemic manifestations, following exposure to an offending drug (like anti-convulsants, antimicrobials or anti-inflammatory drugs). It presents with fever, rash, hematological abnormalities & internal organ involvement. Removal of the offending agent & use of systemic glucocorticoids are the cornerstones of treatment.

Case Report: An eight-year-old boy, on treatment with phenytoin (for generalized tonic-clonic seizure which had occurred 8 weeks ago), presented with- fever, rash, periorbital swelling & pedal edema. Examination revealed bilateral cervical lymphadenopathy, pedal edema & erythematous maculo-papular rash (on abdomen, back, upper & lower limbs) with peeling & erosions over the lips & angle of mouth. Blood investigations showed leukocyte count of 13,600 cells/cumm with eosinophilia (absolute count- 1,632/cumm), elevated liver transaminases (SGOT- 146 IU/L; SGPT- 78 IU/L) & renal failure (elevated BUN- 18 mg/dl & creatinine- 1.1 mg/dl). Renal biopsy suggested interstitial nephritis. Phenytoin was discontinued on suspicion of DRESS syndrome. Patient was treated with oral steroids & hemo-dialysis (for the rising creatinine). Anti-epileptic drug was changed

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to levetiracetam. The patient recovered in 4 weeks. Parents were counselled about risk of reaction to similar drugs & advised regular follow-up to watch for relapse.

Conclusion: DRESS syndrome (although rare in children) should be considered, especially if history of recent addition of potentially incriminated drugs exists. Most patients with DRESS recover completely in few weeks to months after discontinuing the offending drug.

KEYWORDS

• School Anti-Seizure • Dermatological • Eosinophilia • Drug-Induced Hypersensitivity • Eosinophilia Phenytoin • Rash

INTRODUCTION

DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) syndrome is a potential life-threatening illness with cutaneous and systemic manifestations, following exposure to an offending drug (like anti-convulsants, anti-microbials or anti-inflammatory drugs).[1] It presents with fever, rash, hematological abnormalities & internal organ involvement.[1] Removal of the offending agent & use of systemic glucocorticoids are the cornerstones of treatment.[2]

CASE REPORT/ DETAILS

An eight-year-old boy, was brought to the pediatric emergency room with complaints of fever, cough and cold since past 7 days. This was followed by generalized, maculo-papular rash, associated with peeling and desquamation over the hands and feet. There was associated bilateral pedal edema, without any diurnal/postural variation. There was absence of history of vomiting, abdominal pain, bleeding manifestations, joint pains, oliguria or hematuria. The patient had a significant past history of seizures, 2 months ago, which were generalized tonic-clonic in semiology, and treatment was started with phenytoin for the same at a nearby hospital. The seizures were controlled on phenytoin. When the patient presented to our institute, he was on tablet Phenytoin (5 mg/kg/day in 2 divided doses) since 8 weeks. Electroencephalography (EEG) studies and Magnetic Resonance Imaging (MRI) were advised (by the previous hospital). Antenatal and birth history was uneventful, and there was no relevant significant family history.

On arrival in the emergency room, child was sick-looking, with a heart rate of 108 beats/min, respiratory rate of 24 cycles/min, blood pressure of 100/62 mm Hg and the hemodynamics were stable. Examination revealed bilateral multiple cervical lymphadenopathy, the largest node measuring 1.5 cm, firm in consistency, non-matted & not fixed. There was bilateral pedal edema involving the lower one third of leg. Erythematous maculo-papular rash was noted, extending over abdomen, back, upper and lower limbs, associated with peeling of skin over face, dorsum of hands and feet. There was erosion and crusting over lips and angle of mouth (Fig. 1). Systemic examination revealed soft, non-tender hepato-splenomegaly (liver 11 cm, spleen just palpable). Rest of the systemic examination was unremarkable.

On reviewing the history, the patient was investigated along the lines of atypical Kawasaki Disease and drug reaction (Stevens-Johnson syndrome). The complete blood count showed a hemoglobin level of 10 gm/dl, white-blood-cell count of 13,600 cells/cumm (neutrophils - 38%; lymphocytes - 59%) and platelets of 2.8 lakh cells/cumm. The percentage of eosinophils was elevated (12%) with an absolute eosinophil count of 1,632 cells/cumm. The liver function tests revealed elevated hepatic transaminases with SGOT of 146 U/L and SGPT of 78 U/L. The details of preliminary investigations on admission and on day 7 at our hospital are enlisted in Table 1.

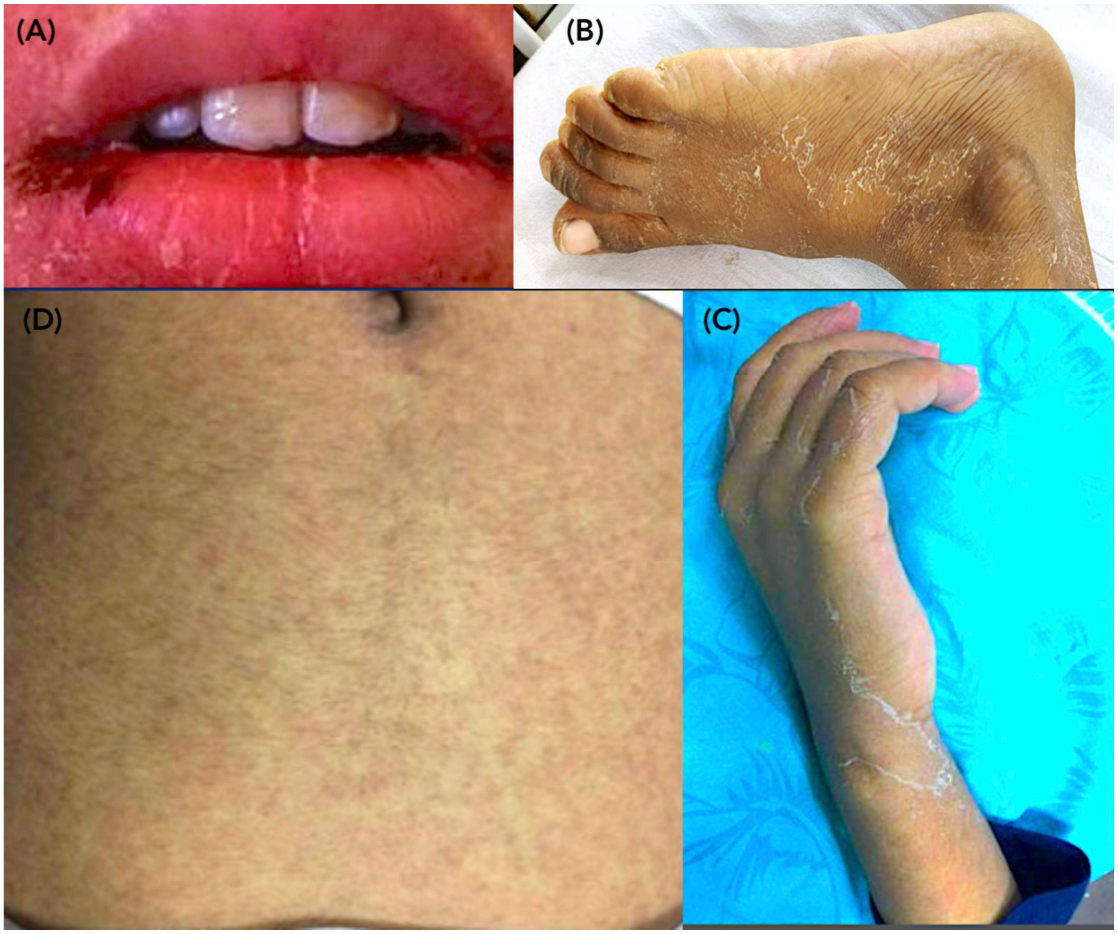

Fig. 1: Examination findings in our patient (clockwise from above left), **(A)** Erosion and crusting over lips and angle of mouth, **(B)** Skin peeling over feet, **(C)** Skin peeling over hands, **(D)** Maculo-papular rash over the abdomen

Table 1: Investigations on admission to the hospital and on Day 7

Investigation Parameters	On Admission	On Day 7	Age-appropriate reference range
Hemoglobin (g/dl)	10	11	(10.5–14.0 g/dl)
Total leukocyte count (cells/mm^3)	13,600	21,600	6.0-14.0 X 10^3 cells/mm^3
Absolute Eosinophil Count (cells/mm^3)	1,632	1,944	50-250 cells/mm^3
Platelet count (cells/mm^3)	2,80000	5,00,000	150-400 X 10^3 cells/mm^3
Serum electrolytes			
Na+	136	129	134–144 mEq/L
K+	4.3	4.7	3.5–6.1 mEq/L
Blood urea nitrogen (mg/dl)	7	18	5–18mg/dL
Serum Creatinine (mg/dl)	0.5	1.1	0.22–0.50 mg/dL
Aspartate transaminase (U/L)	146	189	15–50 IU/L
Alanine transaminase (U/L)	78	132	5–45 IU/L
Blood Culture & Urine Culture	Negative	—	—
Erythrocyte Sedimentation Rate	5 mm/hour	—	<20 mm/hour
C Reactive Protein	64	—	< 10 mg/dl

In view of clinical suspicion of Kawasaki disease, intravenous immunoglobulin was administered and aspirin was started. 2D-echocardiography done showed absence of coronary involvement (aneurysm/s). Additionally, suspecting a possible drug reaction, phenytoin was withheld and anti-seizure medication was switched over to tablet Levetiracetam (20 mg/kg/day in 2 divided doses). On 7th day of hospital stay, the child

started developing periorbital and pedal edema with oliguria. Renal function tests revealed a blood urea nitrogen (BUN) of 18 mg/dl and serum creatinine of 1.1 mg/dl, with a progressively rising trend (to up-to maximum of 71 mg/dl and 6.1 mg/dl of BUN and creatinine respectively). The child underwent 2 cycles of hemodialysis, after which the blood urea nitrogen and serum creatinine fell to 15 mg/dl & 0.5 mg/dl respectively. Renal biopsy (done on 11th day of hospital admission) was suggestive of mild interstitial inflammation with tubular injury.

With the clinical spectrum of fever, rash, eosinophilia, hepatitis, acute renal injury, and history of recent drug exposure, a clinical diagnosis of DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) syndrome, was made. The child was treated with oral steroids (tab prednisolone 2 mg/kg/day in 2 divided doses for 2 weeks) followed by slow tapering over 4 weeks. Improvement in urine output & hemodynamic parameters was noted on day 12 of admission. Fever, eosinophilia, oral crusting & skin lesions subsided in 6 days. The patient recovered completely in 4 weeks. Parents were counselled about risk of possibility of reaction to similar drugs & advised regular follow-up to watch for relapse.

DISCUSSION

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome is a rare, adverse, idiosyncratic reaction to the offending drug, with muco-cutaneous and systemic manifestations. It is characterized by fever, rash, lymphadenopathy, and hematological abnormalities like eosinophilia.[1] The symptom-onset is usually within 2-8 weeks of introduction of the drug. Anticonvulsants (mainly phenobarbitone, phenytoin, and carbamazepine), allopurinol, and sulfonamides are the common triggers.[2] In the pediatric population, antibiotics are reported to be the causative agent for up to 30% of the cases.[2] Amongst the antibiotics, vancomycin, trimethoprim-sulfamethoxazole and amoxicillin are commonly used probable causative agents.[2] Pathophysiology of DRESS syndrome can be attributed to 3 key components-1) genetic susceptibility of certain alleles of the human leukocyte antigen (HLA); 2) modification in the metabolic pathways of drugs, mainly anticonvulsants; and 3) reactivation of HHV 6, which leads to an inflammatory response mediated by T-lymphocytes resulting in tissue damage.[3,4] Anti-seizure medications such as phenytoin, phenobarbitone, carbamazepine, oxcarbazepine, and lamotrigine, are metabolized by hepatic cytochrome P450 enzyme system.[3,5] Defect in the detoxification function can lead to the production of reactive oxygen radicals, which accumulate, cause cellular toxicity, and activate the T-lymphocytes to induce an immune response.[3]

DRESS syndrome has a wide clinical spectrum. The symptoms onset is within 2–8 weeks after drug introduction and may persist for several weeks after drug suspension.[1] In children, the most common clinical presentation is fever, maculo-papular rash, lymphadenopathy with associated eosinophilia.[6] Mucosal involvement, such as conjunctivitis, oral, and/or genital mucositis, can occur as well.[1] The syndrome has a multi-systemic involvement with organ affection with eosinophilic infiltration.[7] The liver is often affected, manifesting as hepatitis, followed by renal, pulmonary, and splenic involvement.[7] The varied symptomatology and presentation of DRESS syndrome makes it difficult to distinguish it from other close mimics such as drug reactions (Steven-Johnson Syndrome and Toxic Epidermo-necrolysis).[8] The clinical scoring system by the European Registry of Severe Cutaneous Adverse Reactions (RegiSCAR)[9] is the most used for diagnosing DRESS syndrome.In these criteria patients are classified as definite (score > 5), probable (score 4–5), possible (score 2–3), or no DRESS case (score < 2).[9]

The first step in the treatment of DRESS syndrome is the omission of offending drug.[10] In mild forms the treatment is based on supportive measures such as fluids, electrolytes, and nutritional support; use of antihistamines and topical preparations to alleviate the cutaneous symptoms.[10] In moderate to severe disease, systemic corticosteroids at a minimum initial dose of 1 mg/kg/day of prednisone (divided in 2 doses) or equivalent and slow tapering over 3–6 months after clinical improvement, are recommended.[11] In patients who are non-responsive to steroids, second-line therapies include intravenous immunoglobulin and calcineurin inhibitors (cyclosporine).[11]

In cases of severe DRESS syndrome unresponsive to steroid therapy, another therapeutic option to be evaluated is plasma exchange, which contributes to the reduction in circulating cytokine levels. A case report by Durak *et. al*,[12] describes the successful treatment of refractory DRESS syndrome (meropenem induced) with plasmapheresis.[12] Long-term sequelae include autoimmune diseases- hypothyroidism, type-1 diabetes mellitus, systemic lupus erythematosus, systemic sclerosis, adrenal insufficiency, and autoimmune hemolytic anemia, which can occur months to years after the resolution, highlighting the importance of long-term follow-up.[9]

CONCLUSION

DRESS syndrome (although rare in children) should be considered, especially if history of recent addition of drugs exists. Diagnosis of DRESS syndrome requires a high index of clinical suspicion and prompt identification can reduce the risk of mortality and morbidity. Most patients with DRESS recover completely in few weeks to months after discontinuing the offending drug.

Conflict of Interests: None

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