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Case Report

Traditional Chinese Medicine Induced DRESS Syndrome: A Case Report and Literature Review

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Abstract Drug reaction with eosinophilia and systemic symptoms (DRESS) is a rare but potentially life-threatening drug related condition. Anti-epileptic agents and antibiotics are the most common culprit drugs. Delayed presentation and wide variety of clinical presentation make DRESS a diagnostic challenge. We reported a case of DRESS induced by Traditional Chinese Medicine. A detailed drug history with a high index of suspicion remains the key to early diagnosis.

Key words *DRESS syndrome; Hepatic dysfunction; Pleural effusion; Traditional Chinese Medicine*

Introduction

Drug reaction with eosinophilia and systemic symptoms (DRESS) was first described as a life-threatening drug-related clinical syndrome with multi-organ involvement by Saltzstein in 1959, and its name was later defined by Bocquet et al in 1996.[1] Diagnosis of this entity is made by the Registry of International Study Group Investigating Severe Cutaneous Reactions (RegiSCAR) scoring system.[2] Other Diagnostic criteria, such as the Japanese Consensus Group Severe Cutaneous Adverse Reactions (J-SCAR) highlighted the importance HHV-6 reactivation and delayed timing of onset of the DRESS clinical features. Among all the internal organ involvement, hepatic dysfunction (either hepatomegaly and/or elevated liver enzymes) was the most common, which was described in up to 94% of all cases. Lung involvement can be present in up to 50% of patients.[3,4] Severe cases may result in intensive care unit admission and necessitate emergency liver transplantation in patients who develop fulminant liver failure.[5] Mortality ranges from 3% to 10%.[5-7] Relapsing disease has been reported to result in long-term autoimmune sequelae and other significant morbidities.[8,9] Anti-epileptic agents were the most commonly reported culprit drug in the paediatric population, followed by sulphonamide antibiotics.[7] Treatment options include immediate discontinuation of the incriminated drug and systemic corticosteroid therapy. Local paediatric studies are lacking due to the disease rarity. Local case series of DRESS with carbamazepine/co-trimoxazole use has been reported in Hong Kong.[10] This case report serves to describe our positive treatment experience with add-on intravenous immunoglobulin combined with corticosteroid in a severe paediatric DRESS caused by Traditional Chinese Medicine.

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Case History

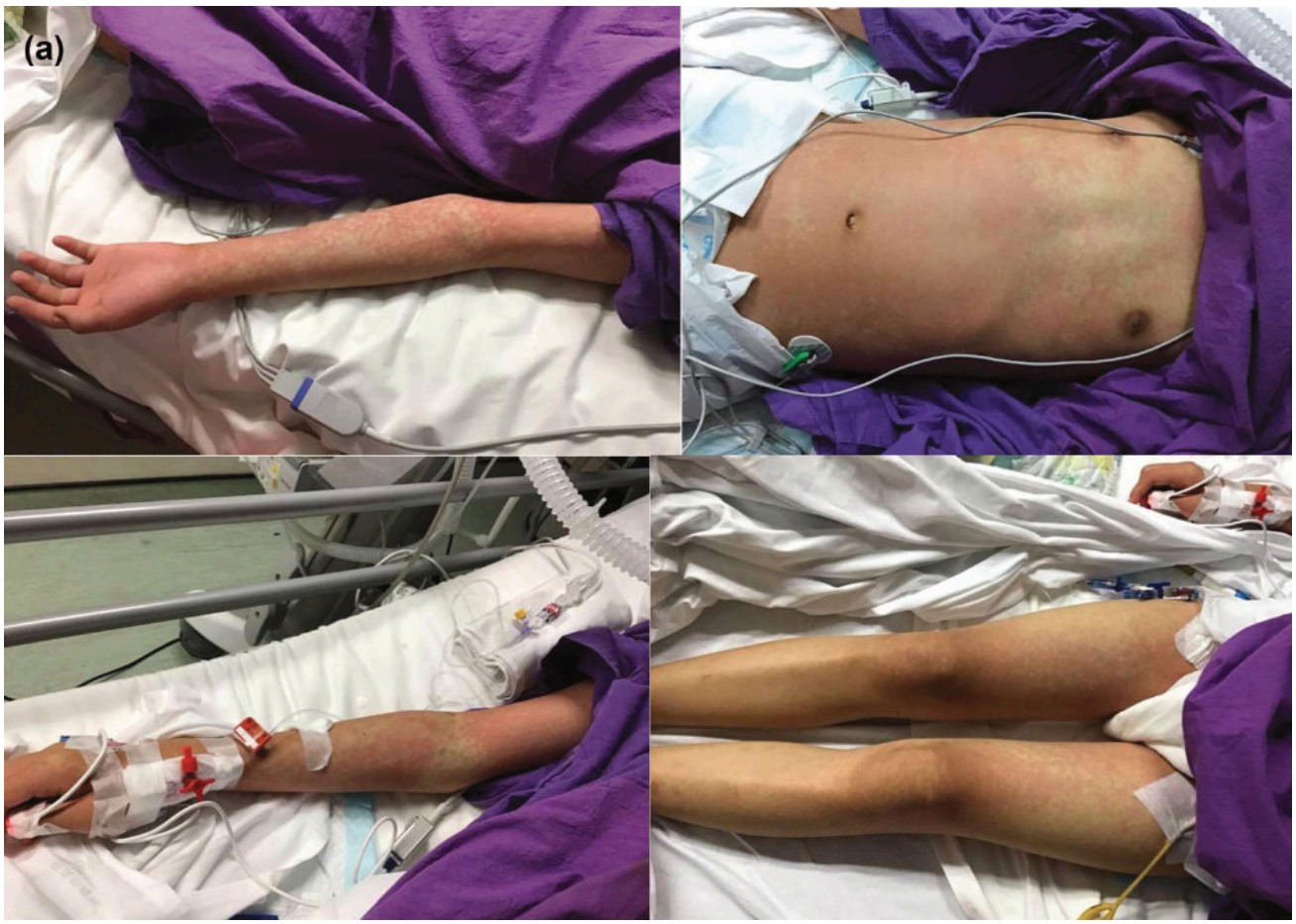
A 16-year-old boy was initially admitted for fever and abdominal pain. Computer tomography of the abdomen showed right duplex kidney with gross hydronephrosis and hydroureter. He was treated as urosepsis with intravenous antibiotics and percutaneous nephrostomy. Subsequently, he was noted to have raised transaminases and mild hyperbilirubinemia. Examination

revealed mild hepatomegaly, bilateral cervical lymphadenopathy and faint erythematous maculopapular rash on the abdomen. The rash progressed in the next few days and became morbilliform with coalescence involving his trunk and limbs (Figure 1a). Nikolsy' sign was negative and there was no other mucosal involvement. Concurrently, he developed respiratory distress and Chest X-ray showed bilateral pleural effusion (Figure 1b), and he was transferred to paediatric intensive care unit for non-invasive respiratory support. Alanine aminotransferase (ALT) gradually rose to 3348 U/L on Day 9 with evidence of hepatic dysfunction (bilirubin 82 umol/L, albumin 23 g/L and pro-thrombin time 18 seconds, and International Normalised Ratio 1.7). Complete blood count showed thrombocytopenia (Platelets 83 x 10^9/L), mild leukocytosis (White blood cell 11.2 x 10^9/L), serum eosinophilia 1.3 x 10^9/L (12.7%) and presence of atypical lymphocytes (6%). C-reactive protein was 18 mg/L. Human Herpesvirus 6 (HHV-6) DNA was detected in serum nucleic acid testing. Other infection screening including blood culture, nephrostomy urine culture, nasopharyngeal swab for common respiratory viruses and bacteria (*Streptococcus pneumoniae, Mycoplasma pneumoniae, Legionella*) were negative. Serological tests for Hepatitis A, B, C and E, Epstein–Barr virus, cytomegalovirus and human immunodeficiency virus were negative. Other autoimmune and metabolic workup for hepatitis including serum ceruloplasmin, anti-smooth muscle antibody, anti-liver-kidney-microsomes antibody were unremarkable. Serum paracetamol level was below toxicity level <34 umol/L. He has been in good health until he had his first episode of generalised tonic-clonic convulsion 14 months ago. Computer Tomography of the brain showed no structural abnormalities but one episode of burst of spike and wave discharge was noted over his left frontal and occipital region on electroencephalogram. He was offered a drug-free observation in our neurology clinic for his first afebrile convulsion but subsequently he had defaulted follow up. His seizure recurred three times with similar semiology and he was prescribed with multiple unlabelled Traditional Chinese Medicine powder and multiple vitamin sup-plement tablets in twice daily dosing by a local Chinese practitioner 5 weeks prior to his symptom's onset. He also had a transient faint rash on his abdomen after applying self-purchased over-the-counter massage oil "Huo Luo You" for abdominal pain. There was in-significant travel history and contact history. He received full vaccination for Hepatitis B and there was no family history of chronic hepatitis. A diagnosis of DRESS was made clinically in view of recent drug use, serum eosinophilia with the presence of atypical lymphocytes, presence of characteristic skin rash and systemic symptoms (haematological, hepatic and pulmonary involvement). The diagnosis was also supported by the Registry of Severe Cutaneous Adverse Reaction (RegiSCAR) scoring system, in which the patient scored 8 out of 9 (Table 1). Systemic screening including echocardiogram, renal function and thyroid function tests were normal. All ten items of the unlabelled Traditional Chinese Medicine powder and the vitamin tablets were sent to the Toxicology Reference Laboratory. The unlabelled powder was later identified to be containing phenytoin and phenobarbital. Phenobarbital was detected in the patient's urine toxicology analysis. The offending agents were removed immediately after admission. He was treated with intravenous methylprednisolone 500 mg for 3 days. In view of severe multi-organ involvement and rising ALT despite methylprednisolone, intravenous immunoglobulin (IVIg) 2 gram/kg divided in 4 days was also given. He became afebrile within 48 hours after steroid administration. ALT gradually improved (Figure 2) and was normalised after one month. His coagulopathy was corrected by intravenous vitamin K and fresh frozen plasma. His ventilation was supported by Bi-level Positive Airway Pressure with maximal inspiratory positive airway pressure of 20 cmH_2O. PaO_2/FiO_2 ratio was all along normal and oxygen therapy was successfully weaned off on Day 12. The pleural effusion resolved with conservative treatment. His rash gradually subsided with residual hyperpigmentation. Oral prednisolone was given after pulse methylprednisolone, which will be tapered in 2 months. He was discharged on Day 21 and had his follow-up appointments in neurology, immunology and dermatology subspecialty clinics. His seizure was controlled with levetiracetam.

Discussion

Great Mimicker

In our case illustration, non-specific symptoms like fever and abdominal pain preceded the characteristic rash and systemic involvement in DRESS. The initial presentation can mimic other diagnoses, including acute surgical conditions, bacterial sepsis, viral-induced hepatitis (especially Epstein-Barr virus), or pneumonia of various infective causes. In retrospect, the hydronephrosis and hydroureter were believed to be an incidental finding



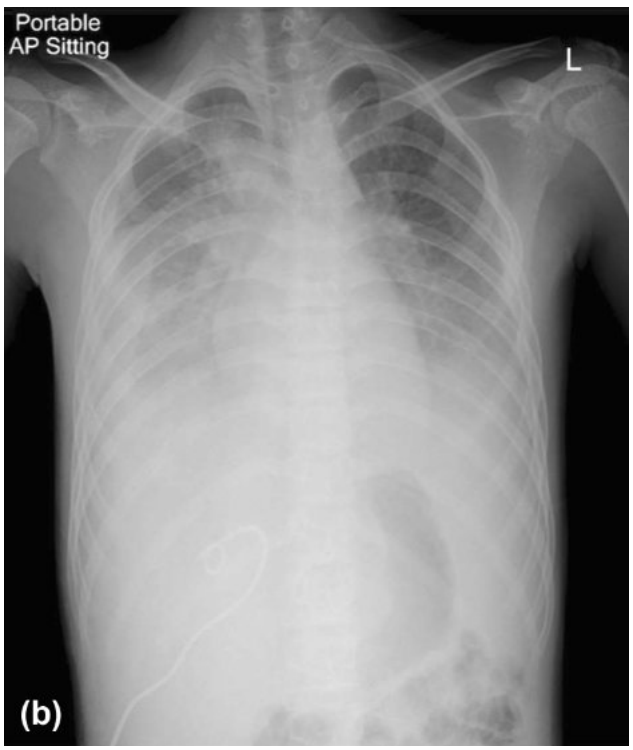


Figure 1 (a) Confluent morbilliform rash with generalised distribution. (b) Bilateral pleural effusion.

related to underlying duplex kidney, and the diagnosis of urosepsis was not established eventually as all the microbiological work up was negative. Haemophagocytic lymphohistiocytosis is an important differential diagnosis due to the presence of persistent fever, cytopenia and raised inflammatory markers. The possibility of paracetamol overdose has been carefully ruled out. Paracetamol was withheld during admission due to deranged liver function. The classically delayed symptom onset from the time of drug ingestion inevitably contributed to diagnostic difficulty. While the characteristic itchy generalised morbilliform rash and serum eosinophilia did suggest drug-related conditions, a high degree of clinical suspicion, together with a detailed drug history and toxicology analysis remain the key to diagnosis. Anti-epileptic agents such as phenytoin, phenobarbital, carbamazepine, and lamotrigine are the most reported culprit drugs of paediatric DRESS.[7] Although various antibiotics including amoxicillin-clavulanate, gentamicin, azithromycin, piperacillin-tazobactam and meropenem were administered to our patient, we believe that none of these were the causative agents as the usage of these drugs do not conform to the traditional timeframe of DRESS onset. Skin biopsy was not performed in our case because of its invasiveness and histological findings could be non-specific. The diagnosis was made solely on clinical grounds with good treatment response.

Prolonged Recovery and HHV-6

Multi-organ involvement was present in our case including hepatitis, pleural effusion, haematological abnormalities and coagulopathy. Hepatic dysfunction is one of the most common systemic involvements in DRESS and can be profound. Acute liver failure was reported to be associated with HHV-6 infection.[11] The exact pathogenesis of DRESS remains unclear but interrelated mechanisms including genetic susceptibility, drug specific T-cell mediated immune response, and HHV-6 reactivation has been suggested.[12] HHV-6 reactivation was included as a defining criteria for Drug-Induced Hypersensitivity Syndrome according to Japanese SCAR criteria. Serum HHV-6 DNA was detected in our case, which may contribute to the disease severity and prolonged recovery.[12] Currently, no United States Food and Drug Administration – approved antiviral protocols exist for HHV-6; and there

Table 1 RegiSCAR scoring system for DRESS, and our patient's score (in bold)

Clinical parameters	Score			Remarks
	-1	0	1	
Fever ≥101.3°F (38.5°C)	No/Unknown	**Yes**		
Lymphadenopathy		No/Unknown	**Yes**	>1 cm, at least 2 sites
Eosinophilia ≥0.7 × 10^9 or ≥10% if leucopenia		No/Unknown	**Yes**	Score 2 points of ≥1.5 × 10^9
Atypical lymphocytes		No/Unknown	**Yes**	
Skin rash				
- Rash suggestive of DRESS	No	Unknown	**Yes**	Suggestive features: ≥2 facial oedemas,
- Extent ≥50% of BSA		No/Unknown	**Yes**	purpura, infiltration, desquamation
Skin biopsy suggestive of DRESS	No	Yes/**Unknown**		
Organ involvement		No	**Yes**	1 point for each organ involvement maximum score: 2
Disease duratio ≥15 days	No/Unknown	**Yes**		
Exclusion of other causes		No/Unknown	**Yes**	1 point if 3 of the following tests are per-formed and are negative: HAV, HBV, HCV, mycoplasma, chlamydia, ANA, blood culture

Total score:-

- <2: Excluded
- 2 to 3: Possible
- 4 to 5: Probable
- ≥6: Definite

are no reports documenting the efficacy of early treatment with antivirals in precluding liver transplant. More studies are needed to better understand the relationship between DRESS and HHV-6.

Positive Experience with Add-on IVIg Therapy

In our patient, fever was subsided, and serum eosinophilia was normalised within 24 hours after methylprednisolone administration.

Although early administration of pulsed intravenous methylprednisolone was associated with good clinical outcome in a prospective study,[13] the benefit on acute liver failure is unproven.[5] In view of persistently elevated transaminases with coagulopathy and multi-organ involvement, IVIg was administered as an add-on therapy. Both adult and paediatric studies have suggested potential benefits of IVIg for steroid hyposensitive DRESS.[14,15] In our patient, ALT level showed prompt improvement within 48 hours after IVIg (Figure 2). Side effects including facial flushing, malaise, haemodynamic disturbances, pulmonary

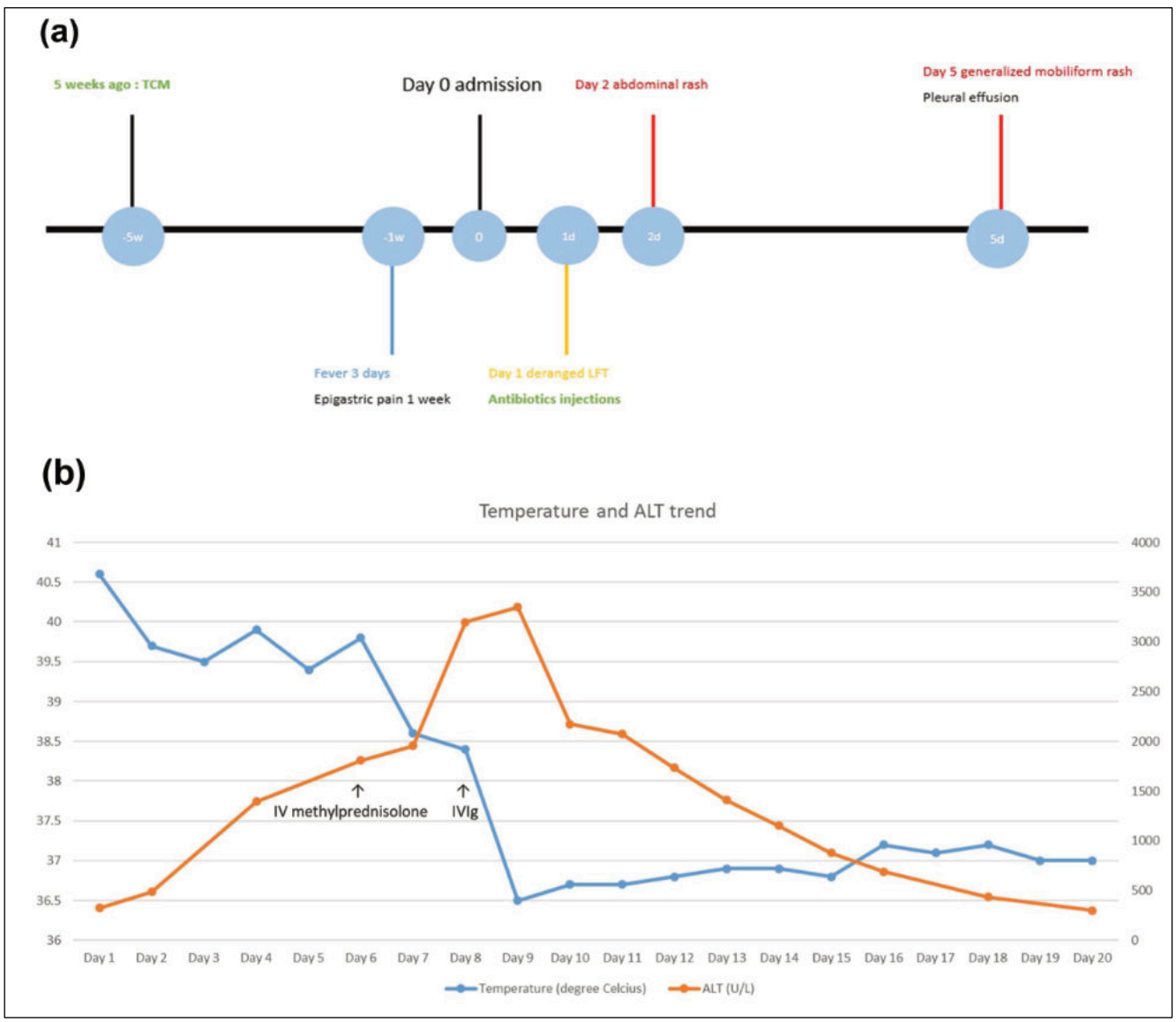


Figure 2 (a) Temporal relationship between the intake of drugs and the onset of symptoms. (b) Treatment response with intravenous methylprednisolone and intravenous immunoglobulin.

embolism have been reported in the literature[16] but none of these were found in our patient.

Concerning other treatment options, other immunosuppressive agents and anti-viral therapy for HHV-6 were not considered in our patient as he demonstrated good response to steroid and IVIg. Combined N-acetylcysteine with corticosteroid use for DRESS has been described with favourable outcome in case reports due to initial suspicion of paracetamol toxicity.[17,18] However, there were no randomised controlled studies to provide conclusive evidence on its efficacy in non-paracetamol-induced acute liver failure.[19] Tofacitinib, a novel therapeutic agent targeting the JAK-STAT-dependent cytokines pathway has been described in 2020.[20]

Prognosis

Regarding the long-term prognosis, our patient requires strict avoidance of aromatic anti-epileptics such as carbamazepine, phenytoin and phenobarbital. Should the patient require anti-epileptics for seizure control, the choice of regimen has to be vigilantly made. Lymphocyte transformation test is a potential tool for in vitro detection of lymphocyte proliferation following drug-specific stimulation to aid the diagnosis of delayed hypersensitivity.[21] Regular follow-up for development of other autoimmune sequelae is necessary. Further studies are needed to delineate the prognostic factors and to guide treatment with the aim to reduce liver transplantation free survival and autoimmune sequelae.

Conclusion

Delayed presentation and wide variety of clinical presentation make DRESS a diagnostic challenge. A meticulously taken drug history with a high index of suspicion remains the key to the diagnosis of this life-threatening condition. Physicians should be alerted to the possible triggering ingredients in Traditional Chinese Medicine. Early diagnosis and prompt treatment are essential for a better patient outcome.

Conflict of Interest

The authors have no conflicts of interest to disclose.

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