A Case of Drug Reaction with Eosinophilia and Systemic Symptoms

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Drug reaction with eosinophilia and systemic symptoms (DRESS) is characterized by fever, skin rash, hematological abnormalities, and systemic involvement such as hepatitis. DRESS usually presents 2–6 weeks after drug initiation. DRESS should be suspected on clinical grounds in the setting of the introduction of new drug therapy and is most commonly described after the introduction of aromatic anticonvulsants, allopurinol, or antiretroviral therapies. We describe here a case of DRESS due to phenytoin exposure with complete resolution on drug discontinuation. Our patient developed DRESS with a skin rash, lymphadenopathy, and markedly abnormal liver enzymes, 4 weeks after drug initiation following drainage of a brain abscess. He was initially diagnosed as having a recurrence of the abscess or sepsis of another origin. It is important to recognize the possibility of DRESS in this setting, as a good outcome depends on the immediate withdrawal of the offending drug. A mortality rate of up to 10% has been described in unrecognised cases.

1. Introduction

Several cutaneous reactions to medication with variable onset and manifestations occur after drug exposure [1]. These reactions are collectively known as SCAR: severe cutaneous adverse reactions to drugs. Drug reaction with eosinophilia and systemic symptoms (DRESS) is a potentially fatal drug reaction characterized by fever, skin rash, hematological abnormalities, and systemic involvement such as hepatitis. DRESS usually presents 2–6 weeks after drug initiation. DRESS should be suspected on clinical grounds in the setting of the introduction of new drug therapy and is most commonly described after the introduction of aromatic anticonvulsants, allopurinol, or antiretroviral therapies. We describe here a case of DRESS due to phenytoin exposure with complete resolution on drug discontinuation. Our patient developed DRESS with a skin rash, lymphadenopathy, and markedly abnormal liver enzymes, 4 weeks after drug initiation following drainage of a brain abscess. He was initially diagnosed as having a recurrence of the abscess or sepsis of another origin. It is important to recognize the possibility of DRESS in this setting, as a good outcome depends on the immediate withdrawal of the offending drug. A mortality rate of up to 10% has been described in unrecognised cases.

2. Case

A 47-year-old male patient presented to a metropolitan hospital with a new onset of fever, headache, right-sided weakness, and dysphasia. His background included a history of paranoid schizophrenia and cannabis abuse. The patient strongly denied the use of injectable drugs. His only medication was long-standing depot risperidone injections. He was a smoker with no known allergies. A computerized tomography (CT) of the brain revealed a 2 × 3 cm mass in the medial left frontal lobe consistent with the diagnosis of a brain abscess. Initial biochemistry and a complete blood count were normal, including liver enzyme tests. Successful neurosurgical drainage of the brain abscess was
Table 1: RegiSCAR criteria for the likelihood of DRESS syndrome.

| No | Yes | Unknown |
|----|-----|---------|
| (1) Fever > 38.5°C | −1 | 0 | −1 |
| (2) Enlarged lymph nodes (>2 sites, >1 cm) | 0 | 1 | 0 |
| (3) Atypical lymphocytes | 0 | 1 | 0 |
| (4) Eosinophilia | 0 | 0 | 0 |
| 0.7–1.49 × 10⁹/L or 10–19.9% | | | |
| >1.5 × 10⁹/L or ≥20% | 1 | | |
| (5) Skin rash | 0 | 0 | 0 |
| Extent > 50% | 0 | 1 | 0 |
| At least 2 of: edema, infiltration, purpura, scaling | −1 | 1 | 0 |
| Biopsy suggestive of DRESS | −1 | 0 | 0 |
| (6) Internal organ involvement | 0 | | 0 |
| One | 1 | | |
| 2 or more | | 2 | |
| (7) Resolution in >15 days | −1 | 0 | −1 |
| (8) At least 3 investigations negative for alternative cause | 0 | 1 | 0 |

Final score: <2 No case; 2-3 possible case, 4-5 probable case; >5 definite case.

undertaken in theatre. Cultures taken from the abscess material grew *Streptococcus anginosus*, and the patient was commenced onto treatment with benzyl penicillin, according to the sensitivities. Phenytoin was initiated as a prophylactic anticonvulsant at an initial dose of 300 mg *nocte*, increased to 500 mg over 2 weeks. Anticonvulsant therapies are individualized within the neurosurgery department according to consultant preference, but the prescribed regime was in keeping with the regional clinical protocol for enteral phenytoin administration. Levels were measured and found to be below the normal range (20 umol/L (normal range 40–80 umol/L)). A week following surgery, the patient was referred to a rehabilitation unit.

Three weeks after admission to the rehabilitation unit (day 27), the patient developed fever (38.4 degrees Celsius). Blood cultures were undertaken, a chest X-ray (CXR) ordered, and a CT scan of his brain repeated which showed a reduced abscess cavity compared to his previous study. A day later the patient developed erythema over his upper torso, malaise and rigors. On the recommendation of the general medical unit on take in the hospital, the patient was commenced on antibiotic therapy (vancomycin), and his biochemistry repeated. The results of the biochemistry revealed deranged liver enzymes (Figure 1) and an elevated CRP (120 mg/L (normal range <8 mg/L)). An ultrasound of the liver was ordered and further blood cultures were taken. His fever persisted and the rash worsened over the following 24 hours. Additionally he was found to have developed lymphadenopathy. The decision was made to transfer the patient to the acute general medical unit within the hospital. After discussion with the on call medical registrar, phenytoin therapy was discontinued. He was also treated with an antihistamine. The rash and temperature persisted, but all cultures remained negative and CXR clear. The liver ultrasound was essentially unremarkable. Additional autoimmune serology was negative. Serology for hepatitis A, B, and C as well as CMV, EBV, and human herpes viruses were also ordered at this point and were negative. The eosinophil count was 0.5 × 10⁹/L (N 0.02–0.05 × 10⁹/L). The patient had rhabdomyolysis with a total CK level of 3485 u/L (N < 250 u/L) and atypical lymphocytes on blood film. The benzyl penicillin was discontinued, after which the patient rapidly improved with complete resolution of fever within 24 hours and clearing of his rash. Liver enzymes remained elevated, but decreased and eventually returned to complete normality 42 days after becoming elevated (Figure 1).

3. Discussion

The patient is presented as a case of DRESS. He expressed typical features of DRESS with skin rash, lymphadenopathy, raised liver enzymes, and atypical lymphocytes, three and a half weeks after commencement onto phenytoin, which is the suspected culprit drug. He did not develop overt hypereosinophilia, which is defined in DRESS as being above 0.7 × 10⁹/L [4], although his eosinophil count was raised above the normal value. He had additional evidence of rhabdomyolysis, which is described rarely in DRESS [7], but is not part of the diagnostic criteria. His RegiSCAR
DRESS in association with human herpes virus type 6 (HHV-6 infection), is suggestive of the diagnoses and may be a cofactor in the pathogenesis of DRESS [8]. An in vitro interferon gamma release test, where serum is exposed to different drugs taken by the patient with a subsequent increase in IFN-gamma demonstrated in the offending drug, can also be performed in cases where there is a clinical necessity to continue drug therapy. This is not yet readily available, but has been described as a useful adjunct in DRESS [11]. There is a high prevalence of cross reactivity to other aromatic anticonvulsants complicating treatment of epileptic disorders in patients with DRESS [12].

Treatment is withdrawal of the offending drug or drugs. Corticosteroids and intravenous immunoglobulins have been given in individual cases [2], but no trials of these therapies exist. The mean time for recovery is 6.4 to 9.4 weeks. Deaths described in the literature were associated with an older age and liver enzyme abnormalities [2].
Our patient fit the criteria for DRESS and showed improvement soon after discontinuation of his phenytoin. He was discharged home from the acute medical ward within a week, following drug withdrawal without the need for further rehabilitative treatment. Levetiracetam was initiated in order to replace the phenytoin. He remained on ceftriaxone at the recommendation of the infectious diseases unit and was followed up in the outpatient department with no recurrence of fever or other symptoms. The patient remained well a year following the above hospitalisation with complete normalisation of inflammatory markers and liver enzymes.

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