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CASE REPORT

A fatal course of brain abscesses attributed to antibiotic treatment

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Abstract

We present a case of a drug reaction with eosinophilia and systemic symptoms (DRESS) in a patient with brain abscesses. The adverse drug event presents with high fever, generalised rash, hypereosinophilia and organ dysfunction. The mainstay of treatment is cessation of the culprit drug, but in our case continuation of antibiotics was essential for the treatment of brain abscesses and alternative antibiotics were hardly, if at all, available.

Introduction

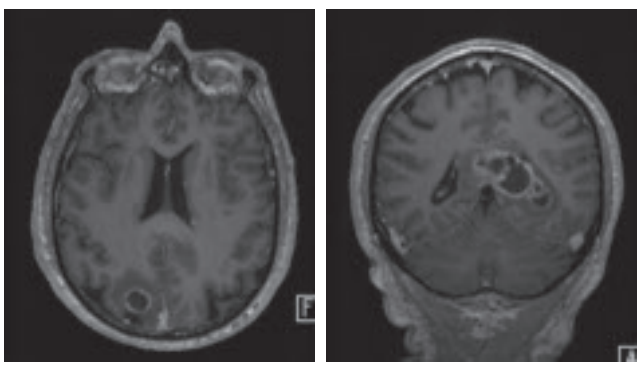
Drug reaction with eosinophilia and systemic symptoms (DRESS) is a potentially life-threatening drug reaction presenting with severe cutaneous eruptions, hypereosinophilia, lymphadenopathy, high fever and internal organ involvement.[1,2] Drug withdrawal is the first action in the management of this potentially life-threatening entity. In general, it is difficult to identify the culprit drug when several drugs have been administered consecutively. It becomes even more challenging when the suspected drug is of paramount importance in the management of an underlying condition. In this case report we present a patient with a fatal course of DRESS secondary to antimicrobial therapy instituted for multiple brain abscesses.

Case history

A 77-year-old male with brain abscesses and multiple organ dysfunction syndrome was transferred to the intensive care unit (ICU) of our university hospital for a second opinion. His recent medical history revealed a visit to his general practitioner nine weeks earlier for annual vaccination against influenza. Within one week he became confused with night sweats and headache. He was treated with clarithromycin 250 mg orally twice daily, without taking cultures for microbiological diagnostic procedures. His symptoms disappeared for one week, but returned. He was admitted to a nearby teaching hospital for further evaluation. Computed tomography (CT) scan of the brain revealed multiple brain abscesses of unknown origin (*figure 1*). No clinical signs of lateralisation or epileptic seizures were reported. Amoxicillin 2 g was given intravenously six times daily as well as ceftriaxone 2 g intravenously twice daily. After thorough assessment, including cultures from the cerebral spinal fluid, blood cultures and transoesophageal echocardiography, no primary site of infection or underlying disease could be identified. The earlier mentioned antibiotics may have prevented the anaerobic microorganisms from being found.

Two days after hospital admission he developed acute kidney injury. Serum creatinine levels increased to 414 mmol/l in combination with a diminished urine production. Under suspicion of drug-induced acute kidney injury, all antibiotics were stopped. Indeed, his kidney function improved after cessation of the antibiotic treatment. In the following days ceftriaxone was restarted and metronidazole 500 mg intravenously three times daily was added. After three days

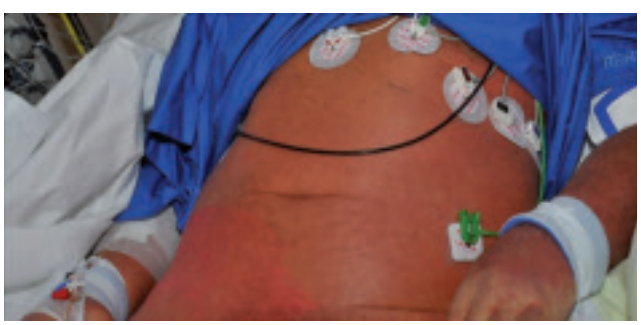
Figure 1. Contrast-enhanced computed tomography of the brain showing multiple brain abscesses.



he underwent an uneventful biopsy of the intracranial lesion. In the following days he developed generalised erythema and pruritus, primarily ascribed to the use ceftriaxone. Microbiological cultures taken from biopsy, while he was being treated with metronidazole and ceftriaxone, showed species from the *Streptococcus milleri* group, susceptible to vancomycin and penicillin. Consequently the ceftriaxone was switched to vancomycin intravenously, guided by plasma concentrations. No anaerobic microorganisms were found. Because of the complicated course, the metronidazole was continued to treat an unrevealed mixed infection with anaerobes. The patient's rash diminished over time. Source assessment for cerebral abscess was repeatedly negative. Five weeks after admission a generalised erythema appeared again, together with the development of dyspnoea, fever 39.9 °C, jaundice and abnormal liver biochemical and function tests. Vancomycin and metronidazole, as possible causatives, were stopped and intravenous penicillin 12 million units every 24 hours was started. Because of progressive organ dysfunction the patient was transferred to the mixed ICU of our hospital. On admission he was disoriented in time, place and person. On physical examination his blood pressure was 90/55 mmHg, heart rate 110/minute, respiratory rate 26/minute and peripheral oxygen saturation 98% with an oxygen supply of 3 l/minute. No heart murmurs were heard on auscultation. His skin showed a confluent erythema with desquamation on both arms and legs (*figure 2*).

The laboratory findings obtained on admission revealed a white cell count of 48.6 x 10^9/l, eosinophils 17%, haemoglobin 5.7 mmol/, platelets 224 x 10^9/l, C-reactive protein 13 mg/l, sodium 137 mmol/l, creatinine 167 µmol/l, alkaline phosphatase 168 U/l, aspartate aminotransferase 1182 U/l, alanine aminotransferase 1046 U/l, gamma-glutamyl transpeptidase 170 U/l, lactate dehydrogenase 1414 U/l, bilirubin 209 µmol/l, prothrombin time > 100 seconds and an activated partial thromboplastin time of > 150 seconds.
Norepinephrine was started to support the haemodynamics. Organ failure progressed with respiratory failure requiring endotracheal intubation and mechanical ventilation. For the management of renal failure we started continuous venovenous haemofiltration with regional citrate anticoagulation. Differential diagnostic considerations for the present fulminant hepatic failure were: drug toxicity, ischaemia, shock, autoimmune hepatitis, infection and DRESS. The consulting dermatologist strongly considered the diagnosis of DRESS, since many of the criteria for DRESS were fulfilled. In the meantime, a CT scan of the brain showed only slight reduction of the brain abscesses, requiring further antibiotic treatment. The antibiotics were again switched, this time to linezolid and gentamicin because the previously started antibiotics could be the possible inducing agents for DRESS as well. Intravenous hydrocortisone 300 mg/24 hours was also administered. His clinical situation rapidly deteriorated into fatal organ failure with haemodynamic instability in spite of maximum supportive measures. Without any therapeutic options, further treatment was discontinued and the patient subsequently died. Permission to perform autopsy was obtained. Histopathology of the skin showed an inflammatory lymphocytic infiltrate with apoptotic keratinocytes matching a drug reaction like DRESS. The lungs showed diffuse alveolar damage. Autolysis was seen in the liver, pancreas, kidneys and adrenal glands. A focus for the brain abscesses was not found. Additional laboratory investigations on virology were all negative for cytomegalovirus, Epstein Barr virus, varicella zoster virus, herpes simplex virus type 1 and 2, human herpes 6 virus and hepatitis A, B and C. Screening for antineutrophil antibodies and antineutrophil cytoplasmatic antibodies was negative as well. No other drugs known for their association with DRESS were administered during the course.

Figure 2. Generalised erythematous cutaneous drug eruption.



Discussion

In this report we present a patient with brain abscesses complicated by a fatal course of DRESS after successive treatment with clarithromycin, amoxicillin, ceftriaxone, metronidazole, vancomycin and penicillin *(figure 3)*. As a consequence of recurrent episodes of skin rashes the antibiotic regime had been changed several times, making it very difficult to identify the culprit antibiotic drug in this patient. Microbiological cultures taken from biopsy of one of the brain abscesses showed species from the *Streptococcus milleri* group necessitating adequate antibiotic treatment despite the concurrent development of DRESS with organ dysfunction. Criteria to fulfil the diagnosis of DRESS were present and were confirmed by post-mortem autopsy. In the case of conflicting interests, so the need for antibiotic treatment versus cessation of the causative antibiotic drug, challenging and difficult choices have to be made.
DRESS syndrome is a rare but serious adverse drug reaction with significant mortality. When visceral organ involvement is present, especially liver necrosis, mortality rates of 10

Figure 3. Duration of antibiotic administration. Onset of rash indicated by red triangles.

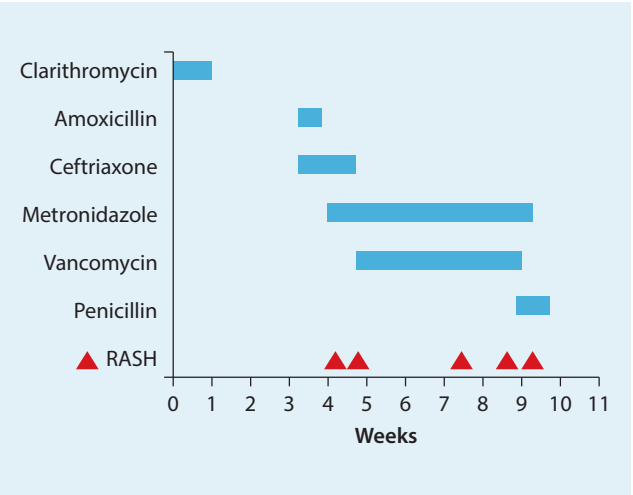


Table 1. Characteristic patterns of drug-induced cutaneous reactions (adapted from Bachot et al.[8] and Husain et al.[9])

Clinical signs	DRESS	TEN / SJS
Onset of eruption	2-6 weeks	1-3 weeks
Duration of eruption	Several weeks	1-3 weeks
Fever	+++	+++
Facial oedema	+++	-
Lymph node enlargement	+++	-
Infiltrated papules	+++	-
Pustules	+	-
Blisters	+	+++
Eosinophils	↑↑↑	normal
Other organ involvement	Interstitial nephritis, pneumonitis, myocarditis	Tubular nephritis, tracheobronchial necrosis
Hepatitis	+++	+
Histology of skin	Lymphocytic infiltrate	Epidermal necrosis

SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis.

to 40% have been reported.[3-5] One of the characteristics of DRESS is delayed onset of disease, two to eight weeks after drug exposure, with relapses or aggravation of symptoms after discontinuation of the causative agent.[1] Anticonvulsants and allopurinol are frequent causatives of the DRESS syndrome, but 44 drugs, including several antibiotics, have been associated with the syndrome.[6]

A scoring system, the Registry of Severe Cutaneous Adverse Reaction (RegiSCAR), to classify DRESS was published by Kardaun et al.[7] The criteria used in this RegiSCAR scoring system are fever, eosinophilia, enlarged lymph nodes, skin involvement, organ involvement, resolution time and exclusion of other potential causes. Patients can be classified as a 'no', 'possible', probable' or 'definite'. It can be difficult to discriminate DRESS from other life-threatening cutaneous drug eruptions. Onset of eruption, histology, visceral organ involvement and laboratory findings may be helpful to distinguish DRESS from Stevens-Johnson syndrome and toxic epidermal necrolysis (*table 1*).[8,9]

The pathogenesis of DRESS is not completely understood. Many drugs, some more than others, can elicit a DRESS response. Virus reactivation, haptenation of endogenous proteins and genetic predisposition are proposed mechanisms playing a role in starting this violent immunological response to certain drugs. Both specific and innate immunity are involved whereby antigens are presented by antigen-presenting cells (APC) to antigen-specific T cells. Recognition of the antigen by the T cell receptor leads to activation and proliferation of antigen-specific T cells and B cells. Antigen-specific B cells can subsequently mature to antibody-producing plasma cells. The T cells, B cells and plasma cells produce cytokines and antibodies that further augment the immune response. Cytotoxic T cells are able to attack antigen-containing cells.[10] According to the Gell and Coombs classification system, DRESS can be classified as a type 4, T cell mediated, delayed drug hypersensitivity reaction.[11] Further subdivision can now be made to classify DRESS as a type 4b reaction, recruiting eosinophils, likely through the production of the cytokine IL-5 by T cells.[12] A factor associated with DRESS is reactivation of human herpes viruses, Epstein-Barr virus, varicella zoster virus and cytomegalovirus.[13] It is unclear whether the viral reactivation is a cause or consequence of the disease. The major proposed pathophysiological mechanism is a cross reaction between virus primed T cells and drug haptenated proteins presented APC eliciting an immune response sustained by continuation of the drug.[14] Recently Camous et al.[13] discussed the immunological concepts regarding haptenation and models of drug-specific T cell activation by binding of drugs or their metabolites to the major histocompatibilty complex (MHC). Haptenation is the phenomenon where an immunologically neutral molecule reacts with a protein structure and so can be presented to the cell surface of an APC to cause a drug-specific T cell response.[13] The drug-specific T cell activation can be provoked by binding of the drug particle directly to the MHC or by binding to the peptides in the MHC groove. Another mechanism of T cell activation is non-covalent binding of the drug particle in the MHC groove.[13,15] There is evidence that medication is metabolised in the APC in a quantity that is enough to stimulate dendritic cells and T cells to provoke an immune response, e.g. sulfamethoxazole.[16] The association between certain human leukocyte antigen allotypes, DRESS and specific drugs suggests that genetic susceptibility is another factor contributing in the pathogenesis of DRESS.[14,15]

The mainstay of treatment in DRESS is immediate discontinuation of the culprit drug. With early cessation of

the detrimental drug outcome is generally favourable, but full recovery from disease may take weeks or even months. Symptoms can aggravate or reoccur in the absence of the causative agent.[6] Unrecognised disease, older age and hepatic involvement with abnormal liver function tests are associated with fatal outcome. Treatment with intravenous and topical corticosteroids is used to suppress the immune system and reduce symptoms from the cutaneous drug eruption. Intravenous immunoglobulins have been used in refractory cases of DRESS. Intravenous immunoglobulins might have an antiviral effect. Santhamoorthy et al. reported a case with clinical improvement, decline of liver enzymes and diminishing of rash after starting intravenous immunoglobulins.[17,18] There is very limited information on the benefits of antiviral therapy in the management of DRESS. Immunological cross reactivity with hypersensitivity reactions may play a part in aggravating or reactivating DRESS.[19] Skin patch testing can be useful to determine the culprit drug and may elicit information on cross-hypersensitivity reactions with other drugs.[20]

In conclusion, whenever a severe cutaneous drug reaction is present, the diagnosis of DRESS must be considered because of the potential fatal course of this syndrome. When the culprit drug is disclosed and the patient requires prolonged and extensive therapy, alternative drugs have to be given. Immunological cross reactivity of drugs and an association with development of DRESS should be taken into account when weighing alternative treatment options. Early multidisciplinary consultation with infectiologists, dermatologists and microbiologists is of great importance to make balanced decisions in precarious situations where conflicting interests of treatment may lead to an unfavourable outcome.

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