Rheumatol Int (2012) 32:2181–2184
DOI 10.1007/s00296-010-1463-9

CASE REPORT

DRESS syndrome with fatal results induced by sodium valproate in a patient with brucellosis and a positive cytoplasmic antineutrophilic cytoplasmic antibody test result

Fatih Albayrak · Serkan Cerrah · Ayse Albayrak · Hakan Dursun · Rahsan Yildirim · Abdullah Uyanik

Received: 8 January 2010 / Accepted: 12 March 2010 / Published online: 31 March 2010

Abstract DRESS syndrome is a life-threatening adverse reaction characterized by skin rashes, fever, leukocytosis with eosinophilia or atypical lymphocytosis, lymph node enlargement, and liver or renal dysfunctions. DRESS syndrome related to valproic acid use is very rarely observed. We present a case of DRESS syndrome induced by sodium valproate, which developed and progressed fatally in a brucellosis patient with a positive c-ANCA test. A 19-year-old female patient presented with fever, cough, jaundice, and rash all over her body. Brucella Coombs test was positive at 1:1280 titers, and the Rose Bengal test was also positive. The involuntary movements were thought to be due to chorea, and the patient was started on sodium valproate 500 mg 2*1, as well as streptomycin 1 g flk 1*1 and tetradox capsules 2*1 for the brucellosis and was discharged. DRESS syndrome was suspected in the patient, and she was taken off sodium valproate and tetradox; N-acetylcysteine, ceftriaxon, prednizolone, and support treatment were started. When sodium valproate is used on its own, it carries no risk of inducing DRESS syndrome. However, in the case presented, another co-morbidity such as brucellosis and c-ANCA positivity was present. We believe that the presence of further co morbidity not yet reported in literature is important from the perspective of the risk of valproate-induced DRESS syndrome. Therefore, if sodium valproate treatment is to be started in patients, especially those with co morbidity, they must be closely monitored with clinical and laboratory observations. At the slightest suspicion of DRESS syndrome, all medication should be ceased immediately and the patient should be placed under continuous observation.

Keywords DRESS syndrome · c-ANCA · Brucellosis · Wegener granulomatosis

F. Albayrak (✉) · S. Cerrah · H. Dursun · R. Yildirim · A. Uyanik
Faculty of Medicine, Department of Internal Medicine, Ataturk University, Erzurum, Turkey
e-mail: fatihalbayrakerz@gmail.com

A. Albayrak
Department of Clinical Bacteriology and Infectious Diseases, Erzurum Region Education and Research Hospital, Erzurum, Turkey

Introduction

Drug rash with eosinophilia and systemic symptoms (DRESS) is recognized as a hypersensitivity syndrome that presents with severe cutaneous eruption, fever, lymphadenopathy, hepatitis, hematologic abnormalities with eosinophilia, and atypical lymphocytes and that may involve other organs [1]. Although the reaction is caused by a limited number of drugs, there are some differences in the clinical and laboratory findings, depending on the drug given, the underlying physiologic state, and the genetic background. Anticonvulsants are the most common cause of DRESS syndrome [2]. However, DRESS syndrome related to valproic acid use is very rarely observed. We present a case of DRESS syndrome induced by sodium valproate which developed and progressed fatally in a brucellosis patient with a positive c-ANCA test.

Case report

A 19-year-old female patient presented with fever, cough, jaundice, and rash all over her body. The patient had been married for 2 years with no children. Approximately

50 days before presenting at the gastroenterology clinic, there were involuntary movements in the left arm and leg and the patient was kept for observation in the neurological clinic. During this period, as a result of the tests carried out on the patient, she was told there was a mitral dysfunction in her heart and that it could be rheumatoid carditis. Furthermore, the Brucella Coombs test was positive at 1:1280 titers, and the Rose Bengal test was also positive. The involuntary movements were thought to be due to chorea, and the patient was started on sodium valproate 500 mg 2*1, as well as streptomycin 1 g flk 1*1 (to be used for 21 days) and tetradox capsules 2*1 for the brucellosis, and was discharged. When she presented to us, she was taking only sodium valproate 500 mg 2*1 and tetradox cap 2*1. On initial evaluation in the gastroenterology clinic, the patient's temperature was 38.9°C, pulse 120 beats/min, respiratory rate 24 breaths/min, and blood pressure 110/70 mmHg. The entire body was covered in a red, raised rash that paled under pressure (Fig. 1). Icterus was present in the sclera and the entire body, the bilateral tonsillae were hyperemic and hypertrophic, there were several lymph nodes with 1 × 1 cm dimensions in the bilateral posterior cervical region, bilateral respiration sounds in the lungs were rough, there was sensitivity in the upper right abdominal quadrant upon palpation, there was a palpable liver (6–7-cm below right medial costal margin), and palpable spleen, a 3-cm below right medial costal margin and bilateral pretibial edema of the spleen. The initial full blood count revealed leukocyte count of 28.8 × 10^9/L (normal range 4.3–10.3 × 10^9/L), hemoglobin 10.9 g/dL (normal range 13.6–17.2 g/dL), platelets 170 × 10^9/L (normal range 156–373 × 10^9/L), neutrophils (PNL) 47.1% (normal range 41–73%), lymphocytes 35.8% (normal range 19.4–44.9%), monocytes 9.6% (normal range 5.1–10.9%), and eosinophils 7.3% (normal range 0.9–6%). The blood smear revealed toxic granulations, PNL 45%, lymphocytes 32%, monocytes 9%, eosinophils 14%, and a few large platelets. Erythrocyte sedimentation rate was mildly elevated at 25 mm/h (normal range 0–20 mm/h). The liver function and coagulation test results are shown in the Table 1. Urea and electrolytes, as well as urine cultures, were unremarkable. Hepatitis B, C, Epstein Barr virus serology, and antinuclear antibody were negative. Cytoplasmic antineutrophilic cytoplasmic antibody (c-ANCA) was positive. No pathological findings were found on frontal and maxillary sinus radiographs. Chest radiography demonstrated a bilateral consolidative and reticulonodular pattern. Lymphadenopathies in the bilateral hilar region and fossa axillaris, bilateral pleural effusion and bilateral

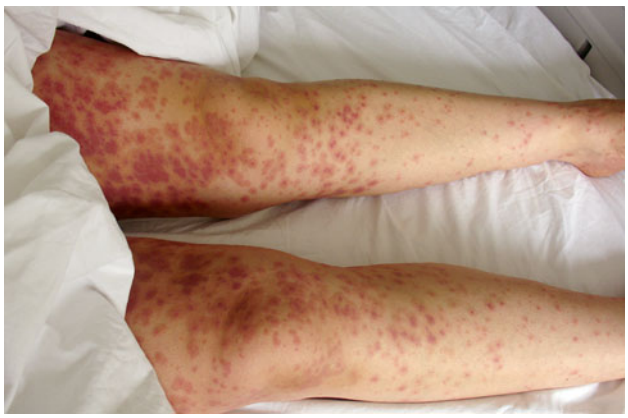

Fig. 1 Generalized erythematous to violaceous maculopapular eruption, and confluent patches with background yellowish skin on lower extremities

Table 1 The liver function and coagulation test results

Test	Reference range	Date						
		Before valproate treatment		After valproate treatment				
		12-06-2009	22-06-2009*	23-07-2009	24-07-2009	27-07-2009	29-07-2009	30-07-2009
AST	<31 U/L	63	50	2,220	2,069	1,206	497	72
ALT	<34 U/L	36	31	695	754	873	523	121
γGT	<38 U/L	16	23	84	71	24		46
LDH	<250 U/L	482	446	1,312	1,216	693	1,047	450
AP	30–120 U/L	67	101	420	377	169		118
T.Bil	0.3-1.2 mg/dl	0.5	0.2	10.5	10.1	15.9	19.9	8.5
Ammonia	<75 μg/dl					124	400	
Albumin	3.5–5.2 g/dl	3.7	3.1	2.1		2.1	2.1	1.0
PT	10–15.9 sn	14.8	14.6	28.9	51.1	77.3	192.4	134.9
PTT	26.5–36 s	27.9	28.1	44	57	64.5	109	154.8

AST aspartate transaminase, *ALT* alanine transfaminase, *AP* alkaline phosphatase, *γGT* gamma glutamyl transferase, *LDH* lactate dehydrogenase, *T.Bil* total bilirubin

* Date of initiation of valproate treatment

interstitial pattern in the lungs were observed in the patient's high-resolution computed tomography (HRCT). In the abdominal computed tomography and ultrasonography scans, there were no anomalies except an increase in liver and bilateral kidney echoes and free fluids in the abdomen. As the general condition of the patient was bad, a bronchoscopy could not be carried out. DRESS syndrome and acute tonsillitis were suspected in the patient, and she was taken off sodium valproate and tetradox, and *N*-acetylcysteine, ceftriaxon, prednizolone and support treatment was started. Methicillin-resistant *Staphylococcus aureus* (MRSA) was determined in the patient's blood culture, and as it was found to be sensitive to vancomycin in the antibiogram, this drug was also included in the treatment. As the Wegener granulomatosis diagnosis was not definite, cyclophosphamide treatment was not started. Despite ongoing therapy, her condition worsened during the following 3 days. On day 4 following transfer, she became encephalopathic. Metabolic acidosis related to respiratory alkalosis and lactic acidosis was determined in the blood gas test of the patient (results of two arterial blood gas tests at 4 h intervals; pH: 7.50–7.39, pO_2: 53–43, pCO_2: 31–28, lactate: 12.2–>15, HCO^{-3}: 24.2–16.9). She was transferred to the intensive care unit for further support. It appeared that her prognosis for recovery with ongoing conservative management was poor. A suitable organ did not become available, and the patient's condition deteriorated during ongoing intensive care. She died 8 days after arriving at the gastroenterology unit.

Discussion

Drug-hypersensitivity syndrome is a life-threatening adverse reaction characterized by skin rashes, fever, leukocytosis with eosinophilia or atypical lymphocytosis, lymph node enlargement, and liver or renal dysfunctions [1]. Bocquet and colleagues proposed the term "drug rash" with eosinophilia and systemic symptoms (DRESS) to simplify the nomenclature of drug-hypersensitivity syndromes (e.g., anticonvulsant hypersensitivity syndrome, phenytoin syndrome, allopurinol hypersensitivity syndrome, dapsone syndrome, eosinophilic pneumonia, exfoliative dermatitis, and drug-induced hypersensitivity syndrome) [3]. The criteria for the diagnosis of DRESS proposed by Bocquet and colleagues are as follows: (1) cutaneous drug eruption; (2) hematologic abnormalities, including eosinophilia greater than 1.5×10^9 eosinophils/L or the presence of atypical lymphocytes; and (3) systemic involvement, including adenopathies greater than 2 cm in diameter, hepatitis (liver transaminases values > 2 N), interstitial nephritis, interstitial pneumonia, or carditis [3]. Liver involvement and eosinophilia generally begin 2–6 weeks after the first drug is administered, that is, later than the skin reactions [4]. Liver involvement is the most common visceral manifestation. Hepatitis characterized by mild hepatomegaly, with or without isolated elevation of liver transaminases, is the most common presentation, but rarely fulminant hepatic failure may occur [5]. Hypereosinophilia probably accounts for involvement of other organs such as interstitial nephritis, pulmonary infiltrates, eosinophilic myocarditis, pericarditis, and thyroid and brain involvement [3, 4]. This multiorgan involvement differentiates this hypersensitivity syndrome from other common cutaneous drug eruptions [5].

Human herpes virus 6 (HHV6) infection associated with anticonvulsant hypersensitivity syndrome and virus-induced immune dysregulation has been reported as a triggering factor for the development of drug rashes, but this was not checked in our case [6].

Anticonvulsant hypersensitivity syndrome/DRESS syndrome is a potentially lethal syndrome that occurs after exposure to aromatic anticonvulsants, including phenytoin and phenobarbital. The incidence of this syndrome induced by these anticonvulsants is thought to be in the range of 1 per 1,000–10,000 exposures. However, DRESS syndrome caused by drugs other than aromatic anticonvulsants has been rarely reported [2]. Valproate is a broad spectrum, non-aromatic anticonvulsant with fewer known adverse effects than phenytoin and carbamazepine. Valproate may induce both dose-related and non-dose-related hepatotoxicity. The typical histopathologic findings of non-dose-related valproate hepatotoxicity are microvesicular steatosis and necrosis [7, 8].

Sodium valproate is very rarely responsible for a hypersensitivity syndrome, but the combination of valproic acid and other antiepileptics (especially, lamotrigine) has been shown to increase the risk of these types of reactions, since valproic acid inhibits the metabolism of other antiepileptic drugs [9]. As far as we know, DRESS syndrome cases related solely to the use of valproate have not been previously reported. DRESS syndrome cases related to valproate use in conjunction with the use of another antiepileptic have been reported, as have cases of co-morbidity with HHV6 infections [7, 10–12]. Although HHV6 was not investigated, our case is the first DRESS syndrome case that has been reported to accompany brucellosis and the presence of c-ANCA. DRESS syndrome cases related to the use of valproate are usually mild; only one pediatric case progressed, as in our case, with fatal fulminant hepatitis. In addition, this is the first case report to describe valproate-induced fulminant hepatic failure occurring as a component of the DRESS syndrome in an adult.

Skin rashes and hepatitis symptoms may be observed in brucellosis. However, the rash is limited, and the hepatitis is not fulminant progressive. Furthermore, the other

components of the DRESS syndrome are usually absent [13, 14]. In the literature, DRESS syndrome has been reported as possible when the use of sodium valproate occurs in conjunction with HHV6 infection [15]. However, there is no research reporting DRESS syndrome with the presence of any other infection. In our case, HHV6 serology could not be investigated. However, our case, whether HHV6 was present or not, was the first DRESS syndrome case emerging in a patient with brucellosis after the use of valproate. We cannot fully explain how brucellosis caused the emergence of DRESS syndrome after the use of valproate. However, we believe that the mechanism that causes HHV6 to trigger the DRESS syndrome may also be valid for brucellosis infection as well [1, 2, 15].

No information as yet exists regarding the relationship of DRESS syndrome and c-ANCA. In our case, there were no findings supporting Wegener Granulomatosis other than the presence of c-ANCA and the interstitial pattern observed in the HRTC. As the patient had to be placed on a mechanical ventilator, the bronchoscopy and biopsy planned for the Wegener Granulomatosis diagnosis could not be carried out. As the WG diagnosis was not confirmed, cyclophosphamide treatment could not be started. The patient was started on prednizolone for the DRESS syndrome.

Conclusion

When sodium valproate is used on its own, it carries no risk of inducing DRESS syndrome. It is only when combined with another antiepileptic, or if HHV6 serology is positive, that the risk of developing DRESS syndrome increases. However, in the case, we are presenting another co-morbidity such as brucellosis and c-ANCA positivity was present. We believe that the presence of further co-morbidity not yet reported in the literature is important from the perspective of the risk of valproate-induced DRESS syndrome. Therefore, if sodium valproate treatment is to be started in patients, especially those with co-morbidity, they must be closely monitored with clinical and laboratory observations, and at the slightest suspicion of DRESS syndrome, all medication should be ceased immediately, and the patient should be placed under continuous observation.

References

1. Sullivan JR, Shear NH (2001) The drug hypersensitivity syndrome: what is the pathogenesis? Arch Dermatol 137:357–364
2. Kano Y, Shiohara T (2009) The variable clinical picture of drug-induced hypersensitivity syndrome/drug rash with eosinophilia and systemic symptoms in relation to the eliciting drug. Immunol Allergy Clin N Am 29:481–501
3. Bocquet H, Martine B, Roujeau JC (1996) Drug-induced pseudolymphoma and drug hypersensitivity syndrome (drug rash with eosinophilia and systemic symptoms: DRESS). Semin Cutan Med Surg 15:250–257
4. Roujeau JC, Stem R (1994) Severe adverse cutaneous reactions to drugs. N Engl J Med 331:1272–1285
5. Kaur S, Sarkar R, Thami GP et al (2002) Anticonvulsant hypersensitivity syndrome. Pediatr Dermatol 19:142–145
6. Mizukawa Y, Shiohara T (2000) Virus-induced immune dysregulation as a triggering factor for the development of drug rashes and autoimmune diseases: with emphasis on EB virus, human herpes virus 6 and hepatitis C virus. J Dermatol Sci 22:169–180
7. Huang YL, Hong HS, Wang ZW, Kuo TT (2003) Fatal sodium valproate–induced hypersensitivitysyndrome with lichenoid dermatitis and fulminant hepatitis. J Am Acad Dermatol 49:316–319
8. Knowles S, Shapiro L, Shear N (1999) Anticonvulsant hypersensitivity syndrome: incidence, prevention and management. Drug Saf 21:489–501
9. Mansur AT, Yasar SP, Goktay F (2008) Anticonvulsant hypersensitivity syndrome: clinical and laboratory features. Int J Dermatol 47:1184–1189
10. Picart N, Periole B, Mazereeuw J et al (2000) Drug hypersensitivity syndrome to valproic acid. Presse Med 29:648–650
11. Plantin P, Cartier H, Le Bihan G et al (1995) Drug hypersensitivity syndrome during treatment with valproic acid. Presse Med 24:1624
12. Zimmerman HJ, Ishak KG (1982) Valproate-induced hepatic injury: analyses of 23 fatal cases. Hepatology 2:591–597
13. Kadanali A, Ozkurt Z, Albayrak A, Ertek M, Parlak M (2006) An unusual presentation of acute brucellosis with fever, jaundice and maculopapular rash. Int J Infect Dis 10:409–410
14. Buzgan T, Karahocagil MK, Irmak H, Baran AI, Karsen H, Evirgen O, Akdeniz H (2009) Clinical manifestations and complications in 1028 cases of brucellosis: a retrospective evaluation and review of the literature. Int J Infect Dis
15. Shiohara T, Iijima M, Ikezawa Z et al (2007) The diagnosis of a DRESS syndrome has been sufficiently established on the basis of typical clinical features and viral reactivations. Br J Dermatol 156:1083–1084