Turk J Gastroenterol *2016; 27: 391-4*

DRESS syndrome in a patient with chronic hepatic encephalopathy

To the Editor,

The drug reaction (or rash) with eosinophilia and systemic symptoms (DRESS) syndrome is an idiosyncratic, uncommon, but severe rare multi-systemic drug reaction that is caused by exposure to antiepileptic drugs, i.e. phenytoin or carbamazepine, primidone and phenobarbitone, with an estimated incidence from 1 in 1,000 to 1 in 10,000 drug exposures (1). It is characterized by at least three of the following features: fever, skin rash, eosinophilia, atypical lymphocytes, lymphadenopathy and hepatitis (2). These alterations can determine a potentially life-threatening condition, distinguished from drug-induced pseudolymphoma (3). The onset is often delayed by 2 weeks and sometimes as much as 2 months after the drug is taken. DRESS syndrome is characterized by the presence of at least three of the following features: fever, exanthema, eosinophilia (>500/μL), atypical circulating lymphocytes and visceral organ involvement, such as lymphadenopathy and hepatitis, typically presenting within 8 weeks of initiation of drug therapy or even later (4).

Here, we report a case of an elderly male alcoholic liver disease patient with a history of chronic vascular-degenerative encephalopathy treated with phenobarbital for alcohol withdrawal syndrome who had a high fever, diarrhoea and a maculopapular pruritic rash that appeared 4 weeks later. The patient provided written informed consent.

A 74-year-old man was admitted to our inpatient clinic for high fever (40°C) associated with diarrhoea, mental confusion and extensive maculopapular pruritic rash that appeared 30 days earlier. The patient was a heavy drinker. One month ago, he had been hospitalized in an Internal Medicine Department for alcohol withdrawal syndrome complicated by an episode of generalized seizure and a history of chronic vascular-degenerative encephalopathy. At that time, he started prophylaxis with phenobarbital. Ten days later, during the same hospital stay, he developed pneumonitis in the lower left lobe, which was treated with ceftriaxone and levofloxacin. After a few days, he developed a *Clostridium difficile* gut infection, which was treated with metronidazole. At the same time, deep vein thrombosis of the lower left limb appeared and was treated with dalteparin. After another few days, a diffuse erythematous rash appeared; metronidazole was then discontinued. The consequent amelioration of skin lesions led to the conclusion that they had been caused by metronidazole treatment. After discharge, treatment was as follows: dalteparin, phenobarbital, lansoprazole, furosemide, folic acid and methylprednisolone. Upon admission to our Internal Medicine Department, the patient appeared confused and dehydrated. A pruritic diffuse erythema associated with severe scratching lesions and mild oedema of the lower limbs were observed. The chest X-ray showed pneumonitis of the lower right lobe and the middle left lobe. Blood tests revealed neutrophilic leucocytosis (leucocytes 11.1*109/L; neutrophils 9.04*109/L) and a slight serum creatinine increase (Table 1). Broad-spectrum antimicrobial (meropenem and teicoplanin), antihistaminic (hydroxyzine hydrochloride) and supportive therapy was administered; however, the fever and erythematous rash persisted. Electroencephalography and brain magnetic resonance imaging did not show any acute pathologic findings. Cardiac ultrasound excluded the presence of valvular vegetations. Blood and urine culture results were all negative, repeatedly. After 14 days, a computed tomography (CT) scan of the chest with contrast media (performed with steroidal pre-medication) showed resolution of the pneumonitis with the presence of chronic peribronchial inflammation.

Because of the possible presence of an adverse drug reaction, we substituted dalteparin with fondaparinux. A new broad-spectrum antibiotic treatment (azithromycin and piperacillin-tazobactam) was set.

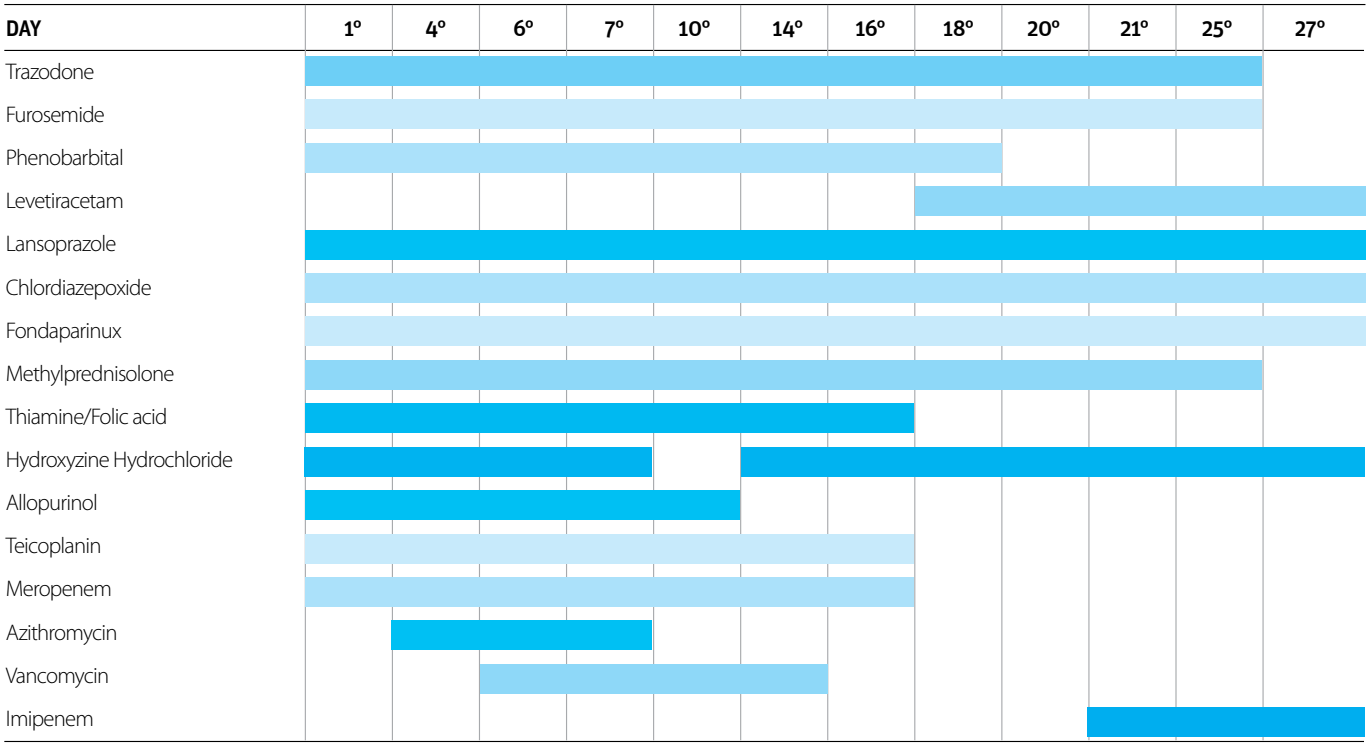
Marked improvement in the clinical conditions of the patient was then registered, including maculopapular rash amelioration and a complete recovery of the neurological status. Biochemical tests showed a resolution of leucocytosis and a reduction in creatinine serum levels. After a

Table 1. Pattern of biochemical parameters during the clinical phases of hospitalization

	1°	2°	4°	5°	7°	8°	11°	16°	17°	18°	19°	23°	25°	37°
Fever (°C)	37.4°	38.2	39.9°	36.8°	36.8°	36.8°	37.4°	37.4°	37.9°	36.6°	37.0°	37.0°	37.0	36.5°
Leukocytes														
(109/L)	11.1	10.2		12.2	13.1	9.93	9.70	9.53	10.5	10.7	7.71	13.3	7.84	9.57
Neutrophils														
(109/L)	9.04	8.67			7.9	5.36	5.38	6.16	5.99	5.47	4.75	10.35		5.23
Eosinophils														
(109/L)	0.11	0.05			2.23	1.59	1.47	1.27	1.68	1.85	1.16	0.8		0.55
Lymphocytes (109/L)	0.92	1.22			1.69	1.95	2.0	1.42	2.0	2.33	1.18	1.22		3.07
S-Creatinine (mg/dL)	1.30	1.30			1.26	1.30	1.35	1.35	1.42	1.72		1.02	1.00	0.96
LDH (U/L)	164								288					
CPK (U/L)	361								478					
CRP (mg/L)		133								28				
AST (U/L)	29	31						14						
ALT (U/L)	11	21						7						

LDH: lactate dehydrogenase; CPK: creatine phosphokinase; CRP: C-reactive Protein; AST: aspartate aminotransferase; ALT: alanine aminotransferase

Table 2. Scheme of treatments used during hospitalization



few days, re-onset of high fever (around 38°C) was observed, together with profuse diarrhoea. Both the toxin and antigen tests for *Clostridium difficile* infection were positive; therefore, the actual antimicrobial treatment was shifted to oral vancomycin therapy, resulting in rapid and complete recovery of diarrhoea in a few days. However, we noted the persistence of fever and the worsening of maculopapular erythema. Blood tests showed eosinophilic leucocytosis (leucocytes 13.1*109/L; eosinophils 2.23*109/L) and increased serum creatinine levels. The other serological tests for *Entamoeba histolytica*, *Leishmania*, adenovirus, *Chlamydia pneumoniae*, *Coxiella burnetii*, *Mycoplasma pneumoniae*, *Strongyloides stercoralis*, *Borrelia burgdorferi*, hepatitis B virus, hepatitis C virus, HIV, *Treponema pallidum* and QuantiFERON were negative.

After 7 days, vancomycin therapy was discontinued following suspicions of reaction to this drug; a *Clostridium difficile* stool test

Table 3. The Naranjo adverse drug reaction (ADR) probability scale

		Yes	No	Do not know or not done	Score
1.	Are there previous conclusive reports on this reaction?	+1	0	0	1
2.	Did the adverse event occur after the suspected drug was administered?	+2	-1	0	2
3.	Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	1
4.	Did the adverse reaction reappear when the drug was readministered?	+2	-1	0	0
5.	Are there alternative causes that could have caused the reaction?	-1	+2	0	2
6.	Did the reaction reappear when a placebo was given?	-1	+1	0	0
7.	Was the drug detected in any body fluid in toxic concentrations?	+1	0	0	0
8.	Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0	0
9.	Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
10.	Was the adverse event confirmed by any objective evidence?	+1	0	0	1
•	Total (>9, definite; 5–8, probable; 1–4, possible; 0, doubtful)				7

at that time was negative. However, the high fever persisted, together with eosinophilic leucocytosis, high serum creatinine and high lactate dehydrogenase levels. A framework of severe global erythroderma associated with exfoliative dermatitis, oedema of the lower limbs and inguinal lymphadenopathy appeared. Analysis of the lymphocytic profile performed to exclude lymphoma showed a depression of the lymphocytic B line.

At this point, the symptoms were thought to result from a hypersensitive reaction, and phenobarbital was withdrawn. We then replaced phenobarbital with levetiracetam as prophylaxis therapy for seizures, and we started treatment with intravenous corticosteroids (Table 2). A rapid and progressive resolution of the symptoms ensued; the fever receded and a significant improvement of the erythroderma and lower limb oedema was observed. Blood tests showed a significant reduction in eosinophilic leucocytosis, creatinine and serum lactate dehydrogenase (LDH) levels. The results persisted even several days after the discontinuation of corticosteroid treatment.

The Naranjo adverse drug reaction probability scale (5) showed a probable correlation (score: 7 out of 10) (Table 3).

The clinical data are in accordance with DRESS diagnosis criteria. In fact, we re-evaluated the patient's medical history, identifying a time correlation between the onset of the erythema and the beginning of therapy with phenobarbital.

The correct diagnosis was delayed by several confounding factors: the allergic reaction was first ascribed to various antimicrobial drugs and then to heparin, which were considered the most likely culprits (usual suspects). Steroids administered as pre-medication for the contrast media CT scan suppressed the symptoms for a few days. The presence of a combination of comorbidities diverted our attention from the main cause of the clinical status of this patient.

In conclusion, we report the first case of phenobarbital-induced DRESS in an alcoholic patient with a history of chronic vascular-degenerative encephalopathy. Moreover, to our knowledge, this is the first case wherein pneumonitis and gut infection are reported together with DRESS syndrome due to phenobarbital. Therefore, this case is highly interesting because it provides a warning for hepatologists regarding the possibility of DRESS syndrome following the administration of phenobarbital.

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Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Universita degli Studi di Firenze.

Informed Consent: Written informed consent was obtained from patient who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - R.G.R., S.G., C.S.; Design - R.G.R, G.S., C.S.; Supervision - G.L., R.G.R., S.G.; Materials - R.G.R., S.G.; Data Collection and/or Processing - T.G., M.M., F.N., V.A., E.T.; Analysis and/or Interpretation - R.G.R., S.G.; Literature Review - T.G., M.M., F.N., V.A., E.T., R.G.R., S.G., C.S.; Writer - R.G.R., T.G., S.G., C.S.; Critical Review - G.L., R.G.R., C.S.

Acknowledgements: Authors would like to thank to Andrea Matucci, MD and Roberto Tarquini, MD.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

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Received: March 25, 2016 **Accepted:** March 31, 2016