

Letters to the Editor

A clinical case of drug hypersensitivity syndrome with phenobarbital administration: drug-induced rash with eosinophilia and systemic symptoms or lupus-like syndrome?

Sirs,

On April 26, 2005, an 84-year-old woman was admitted to our department for syncope. She presented motor aphasia, nuchal rigidity and right hemiparesis. The remaining clinical examination was normal. Brain CT scan evidenced subarachnoid haemorrhagic effusion at the superior cistern, cisterna laminae terminalis and subarachnoid spaces of the left parietal convexity. During the CT exam, she presented a short-term tonic clonic episode, which cleared up spontaneously. Electroencephalography showed diffuse slowing of brain waves. She was treated with nimodipine i.v. and phenobarbital (100mg/day) by oral route: a gradual, clinical improvement, confirmed by brain CT scan, was evidenced. On May 9, she presented continuous, high fever, facial oedema and generalized morbilliform eruption, with pruriginous papules and macules coalescing into larger patches. Laboratory tests revealed anaemia (10.9 g/dl), eosinophilia (15.1 %), an increase of ESR (35mm/first hour) and transaminases (SGOT 56 UI/l, n.v.=5-40 ; SGPT 89 UI/l, n.v.=5-40). An abdomen echography showed mild hepatomegaly with homogeneous structure. A chest x-ray evidenced bilateral pleural effusion. Blood, urine, stool and sputum cultures, and the serological tests for hepatitis viruses, Epstein-Barr virus, human immunodeficiency virus, cytomegalovirus, mumps, rubella, measles, echovirus, coxsackievirus, parvovirus B19, HHV-6, herpes zoster, chlamydia, borrelia, toxoplasma, mycoplasma pneumoniae, mycobacterium tuberculosis and group A streptococcus were performed: they were all negative. On May 11, she presented pulmonary embolism and was treated with heparin infusion. Focalising on the administered drugs, we noted that fever, rash, visceral involvement, and eosinophilia developed about 12 days after the start of phenobarbital treatment. Suspecting a drug-induced systemic syndrome, we interrupted the drug. Further

laboratory tests showed: antinuclear autoantibodies (ANAs) (fine speckled nuclear pattern 1:160, nuclear dots 1:640), Ro/SS-A and Ro/SS-B, screening-lupus anticoagulant (LA), IgA and IgM aCL (respectively, 12.1 APLU/ml, n.v.<10.0; 11.0 MPLU/ml, n.v.<10.0) positive; immunoglobulins, C3 and C4, total B and T lymphocytes, CD4+ and CD8+ lymphocytes, anti-ds DNA, anti-Sm and anti-histone antibodies in normal limits or negative. The patient's HLA haplotype was the following: A2-A3/B51-B52/BW4/CW4-CW6/DR8/DQ4. On May 14, methylprednisolone treatment (40 mg/day) was started. Fever decreased rapidly and the rash disappeared completely one month later. On June 22, she was discharged from hospital in good health and did not present any subsequent recurrence. Our patient satisfies the diagnostic criteria for Drug-induced Rash with Eosinophilia and Systemic Symptoms (DRESS Syndrome), a severe, unexpected reaction to a medicine, starting one to eight weeks after taking the drug and affecting several organ systems contemporaneously (1). The pathogenesis is still unknown: Defects in drug metabolism, and/or a co-infection with HHV-6 (2) are the most quoted hypotheses. Phenobarbital can induce DRESS syndrome (3), not safely Drug-Induced Lupus Erythematosus (DILE) (4). Nevertheless, DILE (1) shares many clinical and laboratory findings with DRESS syndrome (5): a systemic involvement is always present; the disease starts after using the culprit drug; the clinical improvement begins when the drug is discontinued; serum immunological abnormalities are present. Moreover, DILE can be caused by anticonvulsants, except phenobarbital (6): But phenobarbital can induce ANAs positivity (7). At last, some immunological changes were demonstrated in DRESS syndrome: immunoglobulins were normal or increased; complement normal or decreased; ANAs, ENAs and antiphospholipid antibodies present or not (8, 9). Therefore, we asked ourselves: Are DRESS syndrome and DILE really different disorders? Might be they different patterns of the same immunological-mediated systemic drug reaction? How much might genetic assessment and/or environmental factors influence the phenotypic expression of the disorders? The question remains: HLA DR4 predisposes to

DILE (5), while there are no data on HLA antigens in DRESS syndrome; HHV-6 can be implicated in the pathogenesis of DRESS syndrome (2) and perhaps of SLE (10). Our patient did not present HLA DR4 and was negative for HHV-6: May these conditions justify the development of DRESS syndrome rather than DILE? This clinical case offers itself as an occasion for debate.

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References

- BEGON E, ROUJEAU JC: Drug hypersensitivity syndrome: DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms). *Ann Dermatol Venereol* 2004; 131: 293-7.
- SULLIVAN JR, SHEAR NH: The drug hypersensitivity syndrome: what is the pathogenesis? *Arch Dermatol* 2001; 137: 357-64.
- LACHGAR T, TOUIL Y: The drug hypersensitivity syndrome or DRESS syndrome to phenobarbital. *Allerg Immunol* 2001; 33: 173-5.
- ANTONOV D, KAZANDJIEVA J, ETUGOV D, GOSPODINOV D, TSANKOV N: Drug-induced lupus erythematosus. *Clin Dermatol* 2004; 22: 157-66.
- RUBIN RL: Drug-induced lupus. *Toxicology* 2005; 209: 135-47.
- SARZI-PUTTINI P, ATZENI F, CAPSONI F, LUBRANO E, DORIA A: Drug-induced lupus erythematosus. *Autoimmunity* 2005; 38: 507-18.
- ALARCON-SEGOVIA D, FISHBEIN E, REYES PA, DIES H, SHWADSKY S: Antinuclear antibodies in patients on anticonvulsant therapy. *Clin Exp Immunol* 1972; 12: 39-47.
- BARUZZI A, CONTIN M, BARBARA G *et al.*: Drug Rash With Eosinophilia and Systemic Symptoms Secondary to Phenobarbitone. *Clin Neuropharmacol* 2003; 26: 177-8.
- ROUJEAU JC: Clinical heterogeneity of drug hypersensitivity. *Toxicology* 2005; 209: 123-9.
- KRUEGER GR, KLUEPPELBERG U, HOFFMANN A, ABLASHI DV: Clinical correlates of infection with human herpesvirus-6. *In Vivo* 1994; 8: 457-85.