Case Study

A case of drug induced lupus erythematosus after combined treatment with sodium valproate and risperidone

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SUMMARY. The case is reported of a 24 year-old male who presented with fever, eosinophilic pleural effusion and positive antinuclear antibodies (ANAs) in the pleural fluid and blood after long-term combined therapy with sodium valproate and risperidone. These pharmaceutical agents have been implicated singly in the emergence of the syndrome of drug induced lupus erythematosus (DILE). Remission of the symptoms´ and improvement in the clinical and laboratory findings after discontinuation of both drugs strongly suggest that their combination was responsible for the appearance of the syndrome in this patient. *Pneumon 2011, 24(4):436-439.*

Key words:
- sodium valproate,
- risperidone,
- drug induced lupus erythematosus,
- drug induced pleural effusion

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INTRODUCTION

Drug induced lupus erythematosus (DILE) is a clinical syndrome that resembles systemic lupus erythematosus (SLE). It can be caused by the continuous usage of a wide variety of pharmaceutical agents. Most of the manifestations of the syndrome are self limiting and disappear after discontinuation of the pharmaceutical agent responsible[1]. It has been estimated that 15,000–30,000 cases of DILE occur in the US every year[2].

CASE REPORT

A 24 year-old man with mental retardation, who was institutionalized in a care centre for people with special needs, was brought to the emergency department because of persistent high fever (39°C). The patient had been treated for 7 days with an antibiotic (cefprozil 1,000mg per day) with no decline of his fever. His medical history included treatment for several years with sodium valproate for epileptic seizures and risperidone for psychomotor disturbances. No further information could be obtained from the patient because of his mental status.

Clinical examination revealed hypoventilation on auscultation and

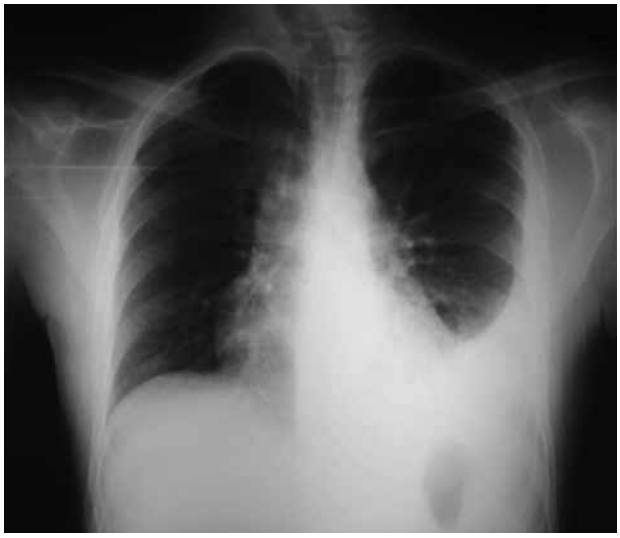

FIGURE 1. At presentation: Pleural effusion at the left hemithorax.

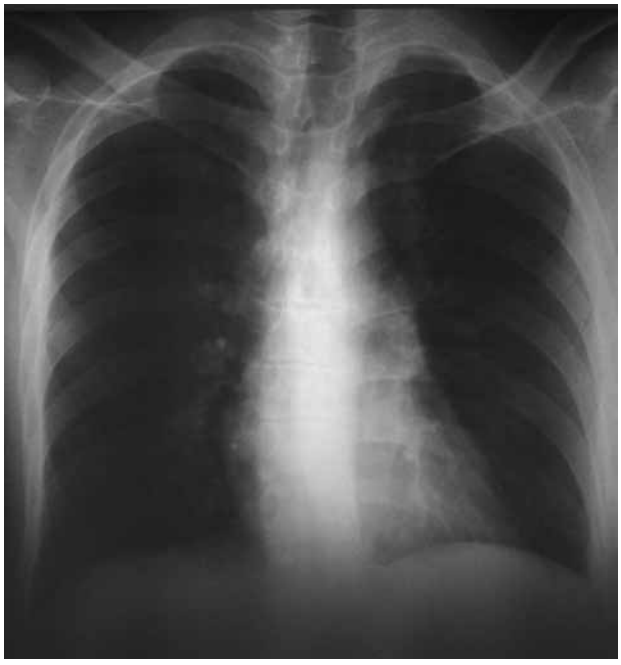

FIGURE 2. Complete remission of radiologic abnormalities at follow up one month later.

increased dullness on percussion over the left pulmonary base. Postero-anterior chest X-ray showed a pleural effusion in the left hemithorax (Figure 1). Diagnostic thoracentesis produced a straw-coloured fluid, with pH 7.14, total cell count 2,500/ml, mainly eosinophils [47%], glucose 20 mg/dl and LDH 1,938 IU/L.

Blood tests showed slightly elevated erythrocyte sedimentation rate (ESR), 69 mm/h and a significant increase in C-reactive protein (CRP), 8.53 mg/dl. Serological testing revealedhomogeneous antinuclear antibodies (ANAs) in a high titer, 1/320 in the pleural fluid and 1/80 in the blood. Anti-histone antibodies were also positive, while anti-double strand (ds) DNA (anti-dsDNA) and anti-extractable nuclear antigens antibodies (anti-ENA) were negative. The tuberculin skin test was negative. Sputum staining was negative for acid-fast bacilli (AFB). Pleural fluid adenosine deaminase (ADA) and the PCR *Mycobacterium Tuberculosis* Direct Test (GEN-PROBE AMPLIFIED, San Diego, CA 92121), cultures of the pleural fluid and gastric aspirate for *Mycobacterium Tuberculosis* were all negative, excluding the diagnosis of tuberculosis. Parasitological examination and blood cultures were negative for pathogens. Pleural fluid cytological examination yielded no positive results and the D-dimers test was also negative.

Two weeks of antibiotic treatment (ceftriaxone 2g once daily in combination with clarithromycin 500mg twice daily and clindamycin 300mg three times, daily followed by piperacillin-tazobactam 4.5 3 times daily in combination with amikacin 500mg twice a day) produced no response. On the basis of the clinical and laboratory findings it was possible to exclude all the usual causes of exudative eosinophilic pleurisy, such as blood or air in the pleural space, infections, tuberculosis, pulmonary embolism, malignancy and autoimmune diseases such as SLE[3],and DILE remained as the most probable diagnosis. Sodium valproate was immediately discontinued and replaced by levetiracetam. The patient showed only slight improvement in clinical symptoms, with partial remission of fever (up to 37.6°C), which continued for a further 16 days. Subsequently, risperidone, the other pharmaceutical agent that was being administered to the patient, was replaced by amisulpride, following which the fever subsided and he was released from hospital on the 41st day. On follow up one month after discharge the patient remained afebrile with no recurrence of the pleural effusion (Picture 2) and with normal blood levels of ANAs.

DISCUSSION

Although there are no definitive and commonly accepted diagnostic criteria for DILE, the following guidelines have been proposed: (*a*) sufficient and continuing exposure to a specific drug, (*b*) at least one symptom compatible with SLE, (*c*) no history suggestive of SLE before starting

TABLE 1. Medications associated with drug-related lupus[7,8]

Drugs definitely associated with drug-related lupus					
Chlorpromazine	Methyldopa	Procainamide	Isoniazid	Minocycline	Quinidine
Hydralazine					
Drugs possibly associated with drug-related lupus					
Acebutolol	Acecainide	Adalimumab	Allopurinol	Aminoglutethimide	Amoproxan
Anthiomaline	Anti-TNF	Atenolol	Atorvastatin	Benoxaprofen	Captopril
Carbamazepine	Chlorprothixene	Chlorthalidone	Cimetidine	Cinnarazine	Clonidine
Diphenylhydantoin	Diclofenac	1-2-dimethyl-3-hydroxy-pyride-4-1	Danazol	Disopyriamide	Enalapril
Estrogens	Etanercept	Ethylphenacemide	Ethosuximide	Fluvastatin	Gold salts
Griseofulvin	Guanoxan	Interferon alpha	Infliximab	Interferon gamma	Ibuprofen
Interleukin-2	Levomeprazone	Leuprolide acetate	Labetalol	Lithium carbonate	Levadopa
Lovastatin	Mephenytoin	Methylthiouracil	Methimazole	Methylsergide	Mesalazine
Metoprolol	Metrizamide	Minoxidil	Nitrofurantoin	Nalidixic acid	Nomifensine
Oxyprenolol	Oxyphenisatin	Penicillamine	Penicillin	Perazine	PAS
Perphenazine	Phenelzine	Phenopyrazone	Phenytoin	Phenylbutazone	Practalol
Pravastatin	Prazosin	Phenylethyl-acetylurea	Primidone	Promethazine	Psoralen
Prophythiouracil	Propafenone	Propranolol	Pyrathiazine	Pyrithoxine	Quinine
Reserpine	Simvastatin	Sulfamethoxypyridazine	Streptomycin	Sulfadimethoxine	Sulindac
Sulfasalazine	Spironolactone	Tetracyclines	Tetrazine	Thionamide	Thioridazid
Tolazamide	Tolmetin	Timolol eyedrops	Trimethadione	Sodium Valproate	

the drug, and (*d*) resolution of symptoms within weeks (sometimes months) of discontinuation of the putative offending agent. In addition, it is frequently suggested that the presence of ANAs is a requisite of diagnosis[4].

Common symptoms of DILE include myalgia syndrome (50% of patients), and arthralgia (90% of patients), which may develop into true arthritis, fever, weakness, fatigue and weight loss. Respiratory symptoms often include pleural pain and pleural effusion[5].

The laboratory findings in DILE include elevated ESR (80% of patients), elevated CRP, anaemia and leucopenia[5], and the serological findings include positive ANAs in 85-95% of patients. Anti-histone antibodies are also positive in more than 90% of cases, compared with approximately 50% of cases with SLE. Conversely, anti-dsDNA and anti-ENA antibodies which are reported in almost 85% of patients with SLE are rarely present in DILE[2]. Positive rheumatoid factor appears in 20-50% of cases of DILE, and hypocomplementaemia (low levels of both C3 and C4) and raised levels of immunoglobins in 10-50%[2,6].

More than 80 drugs have been implicated in the appearance of DILE[7,8] (Table 1). The pathogenesis of DILE remains unclear and current evidence suggestsmore than one mechanism, including: (a) Drugs or their metabolites could bind to proteins and form haptens capable of eliciting T and B cell responses or alter the protein in

TABLE 2: Clinical findings of patients presenting sodium valproate induced pleural effusion

	Fever	Leukopenia	Pleurel effusion	Eosinophilic pleural effusion	ANA's
Tryfon S et al[14]	+	-	+	+	-
Kaufman J etal[15]	-	-	+	+	-
Chiles C et al[16]	+	-	+	+	-
Kravetz JD et al[17]	+	-	+	+	-
Sleiman C et al[18]	-	-	+	-	-
Asconapè JJ et al[19]	-	+	-	-	+
Bleck TP et al[20]	+	+	?		+
Bleck TP et al[21]	-	+	-	-	+

such a way as to make it antigenic[4]; (b) Decreased T-cell methylation results in an overexpression of lymphocyte function–associated antigen (LFA-1). As a consequence T cells with hypomethylated DNA become autoreactive and cause antibody formation[9,10]; (c) Active metabolites of drugs that cause the syndrome can induce cell apoptosis. Cells that have undergone apoptosis contain a large number of autoantigens and when the rate of apoptosis exceeds the rate of clearance[11] it has been observed that ANAs and anti-DNA antibodies can be developed[12]; (d) Drugs responsible for DILE promote the abrogation of self tolerance during T cell maturation in the thymus[13].

Literature review revealed 5[14-18] documented cases of exudative eosinophilic pleural effusion due to treatment with sodium valproate, none of which developed DILE. Four[19-21] case reports were found incriminating valproic acid in the occurrence of DILE (Table 2).

Risperidone is used for the treatment of psychotic disorders and has side effects similar to those of chlorpromazine, which has been implicated in the causation of DILE[22], but no report was found of risperidone as a causative factor of DILE.

Resolution of the symptoms usually occurs after cessation of the suspected drug and is frequently spontaneous, but the time required is highly variable. Rarely, administration of corticosteroids or even immunosuppressive therapy might be required for severe cases of DILE[2,4,23]. The failure of valproic acid discontinuation to resolve this patient's symptoms led to suspicion of the possible involvement of risperidone in the pathogenesis of his condition. This was confirmed by the prompt and total remission of his signs and symptoms within days of discontinuation of both agents. The fact that a month after the replacement of both drugs the patient remained free of symptoms without recurrence of the pleural effusion constitutes evidence of their synergic effect.

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