Eosinophilic pleural effusion secondary to treatment with valproic acid

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To the editor:

Eosinophilic pleural effusion is an entity frequently associated to pneumothorax, hemothorax, malignancy and parasitic or fungal infections[1]. In addition, it has been related with the administration of many drugs, among which four clinical cases have been published in the literature on eosinophilic pleural effusion secondary to the continuous use of valproic acid in patients with neurological or psychiatric condition[1-4].

We present the clinical case of a 19 year old young woman treated with valproic acid who developed eosinophilic pleural effusion. She came to our clinic for the first time due to a probable psychotic picture. Death of her father at 40 years of age due to pulmonary embolism was among the family background. Prior to the present contact, she had not presented medical-surgical background of interest. She smokes 4-5 cigarettes per day. Frequent consumer of cannabis. She denies using other toxic agents.

In December 2003, she came to the emergency service of our hospital, referred from the reference mental health center due to a picture of intense anxiety and significant affective lability. It was decided to hospitalize her for observation and diagnostic assessment, beginning treatment with olanzapine at increasing doses, valproic acid 1000 mg and anxiolytics with slow improvement of her clinical condition. She was discharged at 10 days with diagnosis of bipolar affective disorder, mixed episode with psychotic symptoms.

In February 2004, the patient was admitted urgently to the Internal medicine service due to diffuse, intense abdominal pain, without intestinal rhythm alteration or fever. She also had pleuritic pain in the right rib without dyspnea. No articular clinical data, rash, photosensitivity or oral aphthas were observed. The following clinical signs were observed in the physical examination: apyretic, conscious, oriented. Hemodynamically stable. Cardiac auscultation: without abnormalities. Pulmonary auscultation: hypoventilation in right base. Abdomen: guarding in all the abdomen, more intense in right iliac fossa, with signs of peritoneal irritation. Upper limbs: edema in all the left arm to the hand, no edema on other levels, no active arthritis. It was decided to conduct the following complementary tests that provided the following results: standing out in the complete blood count was leukocytosis with deviation to the left and 212,000/microliter platelets. ESR: 31 mm. Biochemistry, coagulation study and urinary sediment without important pathological abnormalities. CRP: 7.8 mg/l. Negative ANAs, RR, Mantoux. C3 and C4: without abnormalities. Blood cultures: negative. A thoracocentesis was conducted with fluid analysis: glucose exudate 77, proteins 4.2, 5,900 cells with normal cytology and predominance of lymphocytes, ADA 25, LDH 922, C3 and C4 are normal. Negative ANA. Negative BK. Negative Gram and culture.

Right pleural effusion was observed in the chest X-ray. Abdominal ultrasonography: free intraperitoneal fluid with 3 cm left adnexal cyst. The thoracic CT scan confirmed significant pleural effusion with passive atelectasis. After performing a venous doppler in upper left limb, thrombosis of left subclavian with signs of recannalization was observed. The venography of upper left limb described complete thrombosis of left subclavian with organized collateral circulation consistent with old thrombosis, although without ruling our recent rethrombosis. Angio-MRI cerebral: without abnormalities. Treatment was initiated with low molecular weight heparin due to thrombosis of upper left limb, thus resolving the edema of that limb. The course was favorable with improvement of general condition, although right pleural effusion that occupied around 50 % of the hemithorax persisted on discharge.

The previously prescribed psychiatric treatment was maintained and anticoagulation was added as prescribed by the laboratory until new out-patient clinic visit.

Ten days after discharge from the internal medicine service, the patient was readmitted due to thoracic pain. The

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physical examination did not differ from the previous one except for the fact that the abdomen was normal to palpation and not painful. There were no edemas in limbs. Hypoventilation in right base and middle field was perceived on pulmonary auscultation.

The following examinations were added to the previous study: quantification of immunoglobulins (including IgE): normal, VDRL: negative; amoeba, echinococcus and fasciola serology: negative; HBV, HCV and HIV: negative; immunophenotype in peripheral blood: normal, except mild increase of percentage of NK cells. A new thoracocentesis was done: exudate with total proteins 5.6; LDH, 175; ADA, 21; 170 cells with 51% eosinophils and 23 % lymphocytes. Flow cytrometry of pleural fluid without detecting clonality. Negative auramina. Negative culture. Normal ANA, C3 and C4. No pericardial effusion is seen in the echocardiogram. Chest abdominal-pelvic CT scan: massive right pleural effusion with passive atelectasis. Pleuroscopy: microscopically pleura with inflammatory appearance, without visible masses. Negative pleural biopsies.

In the face of this second hospitalization and after reviewing the existing bibliography on this, the diagnostic hypothesis of eosinophilic pleural effusion secondary to treatment with valproic acid was hypothesized, and this drug was discontinued. Six months after discharge, the patient does not present similar symptoms to those previously described.

Up to now, four clinical cases have been described in the medical literature in which treatment with valproic acid has been related with the production of eosinophilic pleural effusion[1-4].

Eosinophilic pleural effusion is defined by the presence of more than 10% of eosinophils in the pleural fluid. Pneumothorax, hemothorax, pulmonary infections, pulmonary infarction and several drugs, among which mesalamine[5], dantrolene, nitrofurantoin[6] and fluoxetine[7] are found are among its causes. It must be remembered that up to one third of eosinophilic pulmonary effusions have an idiopathic cause[5].

Valproic acid is a carboxylic acid classically used as anticonvulsant and more recently in the psychiatric practice as mood state stabilizer.

The final cause of the relationship between eosinophilic effusion and valproic acid is unknown and the diagnosis is presently based on the negativity of the remaining tests conducted and the time relationship of the picture. This is because the symptoms completely disappear after discontinuing the treatment.

In the case of our patients, the negativity of an extensive study conducted and the fact that the effusion did not recur after discontinuing the drug led us to consider the hypothesis of valproic acid as the cause of eosinophilic pleural effusion. The patient continues to be asymptomatic at present.

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