Pericardial and Pleural Effusion with Valproic Acid use in a Patient with Bipolar Disorder

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INTRODUCTION

Valproic acid (VPA) is a commonly used drug in the treatment of diseases such as mood disorders, impulse control disorders, epilepsies and migraines¹. This medication functions by increasing the efficacy of gamma-aminobutyric acid over voltage-gated sodium channels and has different action mechanisms such as effects on the lower units of neural signal transduction. Possible side effects include gastrointestinal symptoms, sedation, hair loss, weight gain, or tremors, and it is known to elevate transaminases in 5-40% of patients. Adverse effects like fetal hepatotoxicity, agranulocytosis and encephalopathy are rarely reported in the literature¹,². It is also reported that pleural effusion (PE) may rarely occur due to the use of VPA³. In the literature, 13 cases of PE developing due to the use of VPA have been reported so far¹¹-¹³. In an animal study investigating teratogenic effect of VPA, the development of drug-induced PE has also been reported¹².

Drug-induced pleural disease is known as a rare condition and is often difficult to prove. The appearance of the effusion may occur within a few hours to 12 years, usually resolving within days after the discontinuation of the drug. A number of cases of VPA-induced PE have been reported although a connection still remains unclear. VPA-induced PE is commonly associated with peripheral eosinophilia although not exclusively, and the effusion may be unilateral or bilateral, resolving on discontinuation of the drug. Some authors emphasize that many PE cases initially
considered idiopathic were actually drug-induced\textsuperscript{1,13}. We report a case of PE in a patient treated with VPA and examine the likelihood that this drug was the cause of the effusion.

Pericardial effusion (PCE) is an ailment that may be life-threatening and seen due to several medical conditions. However, drug-induced PCE is quite rarely witnessed, although cases have been reported associated to the use of anti-carcinogenic medications. In psychiatric medications, clozapine is implicated in reports of drug-induced PCE at a higher rate, compared to others\textsuperscript{14}. We consider that our case was different from others because of both the concurrent development of exudative PE and PCE and the use of VPA.

**CASE**

A 38-year-old male patient was admitted and monitored at our clinic for three years. The case was diagnosed with bipolar I under the DSM-IV diagnostic criteria, and he had been using a combination of VPA 2000 mg/day and risperidone 3 mg/day for one year; he regularly attended our out-patient clinic, and in March 2012, he was referred to an emergency department of a university hospital with complaints of dyspnea and chest pain. Upon physical examination, his body temperature was 36.4°C, pulse rate was 120 beat/min, and arterial blood pressure was 120/70 mmHg. Due to rales in the base of both lungs and deep cardiac sounds, chest x-ray and computerized tomographic angiography (CTPA) were performed; fluid, and PE and PCE were identified, the former in the right and left pulmonary major fissures, and the latter in the bilateral hemithorax. Laboratory tests revealed that the results of arterial blood gas were pH: 7.55; pCO\textsubscript{2}: 22.1 mmHg; pO\textsubscript{2}: 57.6 mmHg; leukocytes: 11300/mm\textsuperscript{3}; troponin: 0.01 ng/mL; D-dimer: 13.15 mcg/mL; and, mass CK-MB: 0.2 ng/mL. In light of these findings, pulmonary embolism and myocardial infarct were excluded; massive PCE was identified, and the case was hospitalized at a cardiologic intensive care unit. PCE diagnosis was confirmed by echocardiography (ECG). Drainer pericardiocentesis was performed. On cytological investigation, no pathology was identified except in erythrocyte and neutrophile cells. Additionally, no reproduction was observed in bacteriologic investigation. On biochemical investigation, the following results were determined in the exudate: protein: 5.3 gr/dL; lactate dehydrogenase (LDH): 469 U/L; glucose: 80 mg/dL; and, chloride: 100 mmol/L. Anti-nuclear antibody and anti-neutrophil cytoplasmic antibody tests were negative. Rheumatoid factor was 20 IU/mL. Erythrocyte sedimentation rate was 24 mm/h. Kidney, liver, thyroid function tests, and serum electrolyte levels were found to be normal. Low hemoglobin (9.78 g/dL) and normal eosinophil (0.22 K/UL) levels were identified with hematologic tests. C-reactive protein (CRP) was found to be 159.42 mg/L, which was higher than normal. After pericardiocentesis, the patient was discharged with the treatment of acetylsalicylic acid (2000 mg/d) and lansoprazole (30 mg/d) as a result of recovery of the clinical symptoms. The case was recommended for follow-ups in the out-patient clinic due to PE and accounted for the fact that the effusion may be due to the use of VPA. Then, he was directed to our psychiatry clinic. After one-month cardiologic follow-up, CRP and hemoglobin levels were seen to return to normal, and myocardial perfusion scintigraphy was done and indicated normal findings. During this period, the patient did not visit our clinic and continued his treatment with VPA by himself. In thoracic computerized tomography, PE in the hemithorax was diagnosed, and the patient was sent to the department of chest diseases with the pre-diagnosis of drug-induced PE. Effusion was investigated by thoracentesis; and the findings were as follows: albumin: 2.5 g/dL; glucose: 70 mg/dL; total protein: 4.6 g/dL; and, LDH: 240 U/L. After the diagnosis of exudates had been established, the case was discharged without suggesting any treatment modalities and was referred for investigation in our hospital with the suspicion of drug-induced PE and PCE by the departments of cardiology and chest diseases. During the follow-up, other medical diseases were excluded via the investigations of the patient admitted to our outpatient clinic in June 2012. VPA
was discontinued because of both continuing PE detected at follow-up performed 3 months later, and because we suspected that PE may stem from the use of VPA. A new treatment with risperidone of 3 mg/day was suggested. In light of clinical examination and consultation with the departments of psychiatry, cardiology and chest disease performed three months later and based on the investigations of chest x-ray and echocardiography, PE was found to have disappeared in the patient, and pleural fluid at minimal level was detected despite almost full reduction in the right hemithorax. During the follow-up after 9 months, no PE and PCE were identified. Because the case was of scientific value, an informed consent was obtained from the patient.

**DISCUSSION**

Cases of drug-induced PE are rarely encountered. It is known that medicines such as VPA, nitrofurantoin, dantrolene, methysergide, amiodarone, fluoxetine and clozapine may lead to PE\(^\text{15}\). The number of case presentations related to the development of PE due to the use of VPA has increased in the literature in recent times. Although the majority of cases with drug-induced PE consist of eosinophilic PE, the development of lymphocytic and transudative PE due to VPA has also been reported\(^\text{7,8}\). In our case, concurrent exudative PE and PCE were identified; however, no eosinophilia was diagnosed. In the literature, although there are various case presentations related to PCE arising from the use of clozapine, the number of cases of drug-induced PCE is very limited. When the literature was scanned, only a pleuropericarditis case associated with the use of VPA was encountered\(^\text{16}\).

Other medical conditions should be excluded to diagnose drug-induced PE or PCE. Pulmonary pathologies were excluded by assessing our patient with chest x-ray and CTPA, and other cardiac pathologies were eliminated with ECG. D-dimer, troponin, and CK-MB from blood tests were within normal limits. Kidney, liver, thyroid function tests, and electrolyte levels were normal, and rheumatologic tests were negative. After performing pericardiocentesis, it was determined that the PCE was of an exudative nature, and there was no malignancy in the cytological investigation and no reproduction including tuberculosis in the microbiological investigation. PE was detected to be exudative with thoracentesis, and so the case was referred to our out-patient clinic with the consideration that the PE might be drug-induced. After reviewing clinical reports and tests, it was decided to continue the treatment with VPA and risperidone regularly, and following pericardiocentesis, PCE, but not PE, was seen to be recovered after three months. VPA was discontinued, and the patient was re-examined at 3 and 9 months; it was determined that PE showed regression, and PE and PCE did not reappear. As no other medical conditions leading to PE and PCE were detected, the PE regressed only after VPA was discontinued, and both PE and PCE did not reoccur, we believe that PE and PCE in our patient were drug-induced.

Multiple drug use increases the risk of adverse drug reactions. In our case, the patient was treated with the combination of VPA and risperidone. To the best of our knowledge, there is no research in the literature showing PE and PCE arising from the use of risperidone. In our case, after VPA was discontinued, it was seen that the PE regressed, and PE and PCE did not repeat during risperidone treatment. Accordingly, we do not consider that PE and PCE were related to multiple drug use and/or the use of risperidone.

The report we have presented is related to a case where PE and PCE occurred concurrently due to the use of VPA. The estimation of the probability of adverse drug reactions is usually based on clinical judgment. However, to determine the probability of adverse drug reactions, Naranjo et al. developed a 10-question scale in 1981, including participants’ responses of Yes, No or Don’t Know. In the scale, each participant is given a total score, and the adverse drug reaction probability is defined according to the total score\(^\text{17}\). When assessed in terms of the
scale, our case received seven points, and so was evaluated as a probable adverse drug reaction.

When diagnosed with drug-induced effusion, and if the patient’s clinical condition permits, the patient can be expected to recover spontaneously. However, there is not enough evidence on whether to re-start the drug or not. As PE in our case continued for three months, the drug was discontinued, and then the PE regressed.

Although how drug-induced PE emerges still remains unknown, there are various assumptions suggesting some factors such as an acute hypersensitivity reaction, a direct dose-related toxic effect, drug-induced inflammation in the pleural space or mesothelial cell injury. In cases where eosinophilia is present when there is eosinophilic effusion, the independence from the duration of drug use and an unclear association with the drug dose highly strengthen the possibility of a hypersensitivity reaction. Our case was regularly using VPA 2000 mg/day for one year and drug serum levels were within normal limits.

**CONCLUSION**

We believe that PE and PCE due to the use of VPA are rarely seen conditions in patients with bipolar disorder. When symptoms such as chest pain and respiratory distress in patients using VPA are encountered, healthcare professionals should be alert for the existence of PE and PCE. After other medical conditions have been excluded, the drug should be discontinued and the course of the PE and PCE should be monitored.

**References:**


