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Valproic acid – induced Pleuro-pericardial Effusion

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Abstract:

***Background*: A medication called valproic acid (VPA) is frequently used to treat a variety of neurological conditions. Common adverse effects include headache, dizziness, tremors, nausea, vomiting, diarrhea, hyperammonemia, thrombocytopenia, and hair loss. Eosinophilic pleuro-pericardial effusion is an uncommon consequence. *Case report:* A 66 years-old male Saudi patient, ex-smoker who had been using valproic acid for 10 years due to epilepsy presented with grade 3 Modified Medical Research Council (mMRC); gradually progressive dyspnea of 10 days duration, dry cough & atypical chest pain. A thorough examination and comprehensive studies revealed the presence of an eosinophilic pleuro-pericardial effusion. After ruling out other possible reasons, valproic acid toxicity and/or overdosage seem to be the primary cause of effusion. Modifications were made to medications. The patient was seen to be fully recovered at the end of the six-month follow-up. *Conclusion:* The most common explanation for valproic acid-induced eosinophilic pleuro-pericardial effusion is a medication hypersensitivity reaction. It is more likely to happen when two crucial elements are present: a high dosage of the drug and prolonged exposure.**

Key words: Eosinophilic, pleuro-pericardial effusion, valproic acid.

Introduction

Numerous neurological conditions, including bipolar disorders, migraines, and epilepsy, are frequently treated with the medication valproic acid (VPA). VPA frequently causes headaches, dizziness, tremors, nausea, vomiting, diarrhea, hyperammonemia, hair loss, and thrombocytopenia[(1).] There are several causes of eosinophilic pleuro-pericardial effusion. Hemothorax, pneumothorax, trauma, post-thoracotomy, infectious diseases, pulmonary embolism, TB, fungal and parasite infections, connective tissue disorders, cancer, asbestos exposure, and certain medications are some of these causes. The exact cause of 14–25% of instances is still unknown[(2,3)]. One of the uncommon adverse effects noted in earlier research is VPA-induced eosinophilic pleuro-pericardial effusion[(4,5)]. VPA toxicity can cause unilateral or bilateral pleural effusion. An effusion with at least 10% eosinophils is known as an eosinophilic pleuro-pericardial effusion[(6,7)]. As an eosinophilic pleuro-pericardial effusion occurs, eosinophilia (a high eosinophil count in the peripheral blood >0.5×10^3/μl) typically occurs and d disappears after the effusion resolves[(8)]. In cases of drug-induced pleuro-pericardial effusion, symptoms typically start to go better a few days after stopping the

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medication and go away entirely in a few months. We represent an elderly man with a seizure problem who was taking VPA. After increasing his dosage, he developed an eosinophilic pleuro-pericardial effusion, which went away after he stopped taking the medication. One excluding diagnosis is drug-induced eosinophilic pleuro-pericardial effusion. To identify a drug-induced reaction, a high index of suspicion and a methodical approach are essential[2].

Case Report

A 66 years-old male Saudi patient, ex-smoker who had been using valproic acid for 10 years due to epilepsy presented with grade 3 Modified Medical Research Council (mMRC); gradually progressive dyspnea of 10 days duration, dry cough & atypical chest pain. The treating neurology physician steadily upped the medicine dosage from 1000 mg to 2000 mg per day six months ago. Levetiracetam 2000 mg/day was added to his treatment regimen for three years in order to better control his symptoms. He did not utilize any drugs or have any other known diseases. His heart rate was 71 beats per minute, his respiratory rate was 30 minutes, his blood pressure was 110/80 mmHg, and his body temperature was 36.8 °C. Upon local examination, Chest auscultation revealed absent breath sounds in the left hemi thorax and dullness on percussion. There were neither additional cardiac sounds nor murmurs.

Neurological examination was normal. Electrocardiography showed normal sinus rhythm.

The chest X-ray and chest tomography showed moderate left-sided pleural effusion as well as pericardial effusion (Figure 1), for which diagnostic drainage under ultrasound guidance was performed, showed characteristics of an eosinophilic exudate (Table 1). A significant effusion was visible in front of the right ventricle on the transthoracic echocardiography (ECO). The fluid's cytological analysis showed no malignant cells, and the results of the Gene-Xpert and acid-fast stain tests for Mycobacterium tuberculosis were negative. There was no departure from the typical levels in the immunological testing. Hemoglobin was 10.6 g/dL and white blood cells were 8230 cells/µL (neutrophil 56.7%, monocyte 16.1%, eosinophil 1%, and basophil 0.3%), according to blood tests and the hemogram. Creatinine was 0.7 mg/dL, blood urea nitrogen was 12.62 mg/dL, aspartate aminotransferase was 30 U/L, alanine aminotransferase was 11 U/L, albumin was 3.25 g/dL, lactate dehydrogenase (LDH) was 112 U/L, protein was 8 g/dL, and albumin was 5 g/dL, according to the findings of the biochemistry test. The levels of thyroid hormones were normal. The typical therapeutic range for VPA is 50–100 µg/mL; the blood level was 183 µg/ml. Pericardiocentesis, and thoracentesis were carried out under strict aseptic conditions in the presence of increasing respiratory distress, under the supervision of an intervention radiology consultant for ultrasound guidance. Thoracentesis from the left thorax yielded 1000 cc of liquid exudative fluid, while pericardiocentesis yielded 750 cc. A study of pleuropericardial fluid showed 65% eosinophils. The effusion's histopathological analysis revealed that it was an eosinophilic substance devoid of any indications of neoplasia. A microbiological analysis revealed no bacterial, fungal, or parasitic illnesses. There was no indication of a pulmonary embolism on chest tomography, and the lung parenchyma was normal. It was believed that medication

toxicity was the cause of the pleuro-pericardial effusion in the patient with a high blood level of the VPA medicine after other medical explanations had been ruled out. The dose of VPA was gradually reduced and ultimately stopped in accordance with neurology guidelines. Lacosamide was given as an adjuvant treatment for seizures, and its dosage was progressively increased to 400 mg per day. The patient was released from the hospital following clinical improvement, a normal chest X-ray, and good physical condition following full therapeutic tapping of the pleural fluid. Levetiracetam (500 mg bid) should be continued, the neurologist stated. Over the course of six months, the patient's clinical, laboratory (VPA blood level), and radiographic (CXR & echocardiography) data all demonstrated full improvement.

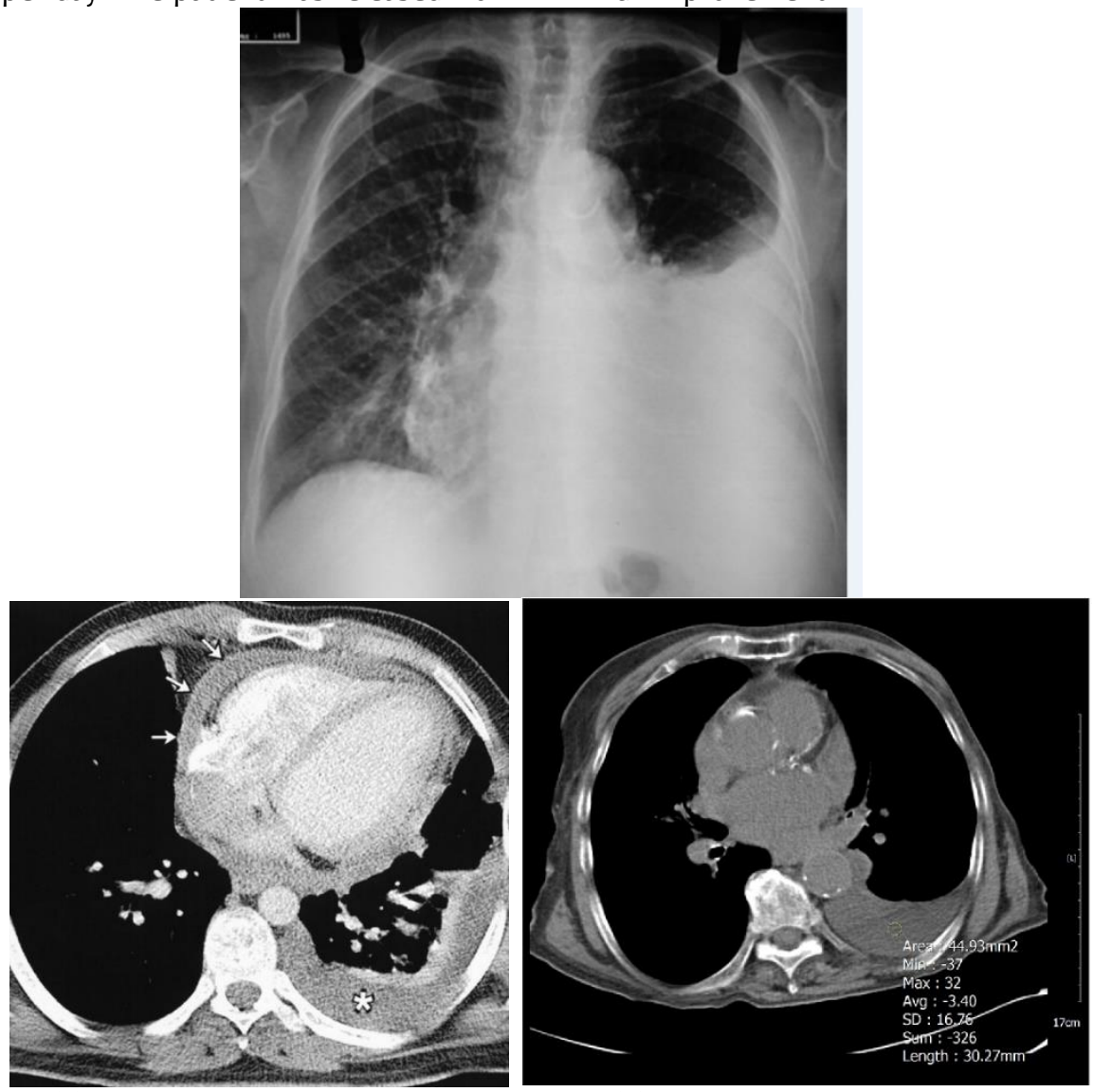

Figure 1. (a) Chest x-ray shows left-sided pleural effusion, (b) Chest tomography shows left-sided pleural effusion and pericardial effusion.

Table 1: Features of pleuro-pericardial fluid in a patient who acquired pleuropericardial effusion while on valproic acid	
Effusion Features	**Pleuropericardial fluid**
Protein (g/dL)	6.40
Glucose (mg/dL)	83
Albumin (g/dL)	3.30
LDH (U/L)	242
WBC count (no. of cells × 1,000/mm3)	2000
Eosinophils	**65%**
Neutrophils	22%
Lymphocytes	13%

Discussion

Rarely, medications such as VPA, acyclovir, bromocriptine, methotrexate, fluoxetine, dantrolene, infliximab, and even some vitamins (B5 and B7) might result in eosinophilic pleuro-pericardial effusion. Eosinophilia in the pleural and pericardial sacs usually develops few months after the initial dose, although this might vary from a few days to 1-2 years or even 12 years[9,10]. Valproic acid-induced pleuro-pericardial eosinophilia has no known mechanism of development, but there are a number of theories that could account for it, including 1) acute hypersensitivity reaction, 2) dose-related direct toxic effect, 3) drug-related inflammation of the pleuro-pericardial cavities, and 4) oxidant-induced mesothelial cell damage[11]. Although our patient has been taking VPA for a long time, the dosage was raised to 2000 mg per day six months ago, and tests conducted during his evaluation for respiratory distress and effusion work-up revealed a blood level of 183 µg/mL (therapeutic range 50-100 µg/mL), indicating a direct toxic effect of the medication. This demonstrates the significance of medication-related pleuro-pericardial effusion in both acute hypersensitivity reaction and drug dose. The eosinophil proportion in our patient was 65% in the pleuro-pericardial fluid study and 1% in the peripheral blood examination. Because there is only a limited link between the percentages of eosinophils in blood and the pleuro-pericardial fluid, laboratory screening of peripheral blood is typically not selective in individuals with eosinophilia in the pleural and pericardial fluid[12]. The patient's chest tomography and echocardiography images were consistent with pleuro-pericardial effusion. Pleuro-pericardial effusion caused by VPA is essentially an uncommon illness that is closely linked to drug toxicity. According to reports, the majority of these instances are either lymphocytic or eosinophilic[13]. As a result, VPA-induced pleuro-pericardial effusion is a potential side effect, and its occurrence is significantly influenced by the drug's dosage and duration. These potential side effects can be anticipated and even avoided with routine medication blood level monitoring during dose increases[14].

Conclusion

Patients with a variety of neurological conditions may get pleuro-pericardial effusion as a result of long-term high dose VPA use. Healthcare providers should be on

the lookout for pleuro-pericardial effusion when patients receiving VPA experience symptoms including chest discomfort and difficulty breathing. Causative medication should be stopped once all other medical diseases have been ruled out, and the progression of the pleuro-pericardial effusion should be tracked clinically and radiologically.

Conflict of Interest The author's stat having no competing interests.

Ethical Approval Informed Consent Written an informed consent form was obtained from the patient for the case presentation and necessary information was given to the family.

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