Case Report

Valproic acid-induced eosinophilic pleural effusion: An uncommon occurrence

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ABSTRACT

A 43-year-old male using valproic acid (VA) for 2 years for seizure disorder presented with right-sided moderate pleural effusion. Pleural fluid analysis revealed exudative effusion with 42% eosinophils. There was no evidence of haemothorax, pneumothorax, malignancy, and parasitic infections. Suspecting a drug-related event, VA was discontinued. The patient showed clinical improvement with resolution of pleural effusion on chest radiograph three weeks later. VA is a popular drug used for variety of disorders like seizures, migraines, and schizophrenia. There is a paucity of literature on VA-induced pleural effusion. Though a rare phenomenon, clinicians should be aware of such a possibility to avoid erroneous diagnosis.

KEY WORDS: Drug reaction, eosinophilia, uncommon

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Submitted: 02-Sep-2022 **Accepted:** 28-Oct-2022 **Published:** 29-Dec-2022

INTRODUCTION

Eosinophilic pleural effusions (EPEs) have multiple aetiologies. The causes include haemothorax, pneumothorax, infectious diseases, connective tissue disorders, tuberculosis, malignancy, asbestos exposure, and some drugs. In 14–25% of cases, the specific aetiology remains undetermined.[1,2] The significance of eosinophils in pleural fluid is unknown. In a systematic review by Oba *et al.*,[3] malignancy (26%) was the most common cause of EPE. EPE can be unilateral or bilateral and may be associated with blood eosinophilia. In a case series on idiopathic EPE, out of 11 patients, 5 were misdiagnosed initially as tubercular, and one each as malignant and congestive heart failure.[1] Drug-induced EPE is a rare entity, especially in the context of valproic acid (VA).[4,5]

Access this article online

Quick Response Code:

Website: www.lungindia.com

DOI: 10.4103/lungindia.lungindia_440_22

The literature on VA-induced EPE is scarce. We report a case of middle-aged male using VA for seizure disorder who developed EPE which resolved after discontinuation of the drug. Drug-induced EPE is a diagnosis of exclusion. High index of suspicion and stepwise approach is the key to detect drug-induced reaction. To the best of our knowledge, this is the first case reported from Indian literature.

CASE REPORT

A 43-year-old non-smoking male presented to the Chest Clinic with chief complaints of cough and breathlessness on exertion for 2 weeks. There was no history of sore throat, fever, weight loss, or loss of appetite. He reported

How to cite this article: Bhardwaj M, Himral P, Kashyap S. Valproic acid-induced eosinophilic pleural effusion: An uncommon occurrence. Lung India 2023;40:82-5.

that he had been on anti-epileptics for focal seizures with secondary generalization since the age of 12. He was initially treated with carbamazepine and was shifted to VA (500 mg twice daily) 2 years back. He was not on any other medications. He was not a diabetic or hypertensive and had no past history of pulmonary tuberculosis. There was no history of joint pains, difficulty in swallowing, dry eyes, or skin changes. His bowel and bladder habits were normal. There was no history of trauma, surgical intervention, prolonged immobilization, or occupational exposure to asbestos or other toxic substances.

Clinical examination revealed that he was afebrile with normal vitals. Baseline blood investigations were unremarkable with a normal total leucocyte count (7,000/μL; eosinophils 2%). A chest radiograph showed right-sided moderate pleural effusion without parenchymal infiltrates [Figure 1a]. A diagnostic thoracentesis was carried out revealing a pale, exudative (protein: 5 g/dL) effusion with eosinophilia (42%), and low adenosine deaminase (18 U/L). Other pleural fluid findings are depicted in Table 1. The ultrasound abdomen was unremarkable. His real-time polymerase chain reaction test of nasopharyngeal swab for SARS-CoV-2 was negative. Sputum for gram stain, acid fast bacilli, and cartridge-based nucleic acid amplification test (CBNAAT) for mycobacteria were also negative. The tuberculin skin test was negative. Further laboratory tests, including thyroid hormones, Rheumatoid factor (RA), and Antinuclear antibodies (ANA) were negative. Blood absolute eosinophil count in blood was 140 cells/μL. The echinococcus IgG antibodies were undetectable. There was no evidence of parasites or parasite eggs in stool or pleural fluid. Based on the above findings, a diagnosis of VA-induced pleural effusion was made. On application of Naranjo criteria, the probable cause of pleural effusion with a score of 7 was drug induced.[6]

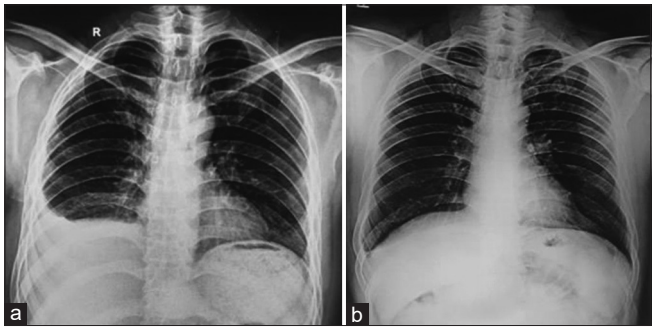

Figure 1: (a): Right moderate pleural effusion; (b): Resolution of pleural effusion 3 weeks after discontinuation of valproic acid

Table 1: Pleural fluid findings

Pleural Fluid
Glucose=60 mg/dl
LDH=669 U/L
CBNAAT=Mycobacteria not detected
Cytology: Malignant cells not detected

	Light's Criteria	
	Protein (g/dl)	**LDH (U/L)**
Pleural fluid (PF)	5	669
Serum (S)	7	248
Ratio (PF/S)	0.71	2.69

LDH: Lactate dehydrogenase, CBNAAT: Cartridge-based nucleic acid amplification test

The drug (VA) was discontinued, and the patient was shifted to alternative anti-epileptic (levetiracetam 500 mg once daily). On follow-up at 3 weeks, his symptoms had improved and pleural effusion had resolved [Figures 1a and b]. The patient remained asymptomatic with no evidence of refilling on either side at repeat follow-up after 1 month.

DISCUSSION

VA is a well-known drug widely used for several seizure disorders. Other indications are bipolar disorder and psychotic disorders like schizophrenia and migraine. Recently, it is being explored as an adjuvant therapy for cancer, HIV, and neurodegenerative diseases. It is commonly associated with adverse effects like nausea, vomiting, tremors, sedation, weight gain, hepatic failure, and teratogenicity.[7]

VA associated pleural reaction is a rare entity. Our case had unilateral, exudative EPE with normal peripheral blood eosinophils. In a brief review, Bullington *et al*.[8] (2007) revealed that VA-induced EPE could be unilateral or bilateral, exudative or transudative, and pleural or blood eosinophilia is not a regular feature. However, it was noted that most of the patients reported in this review were on multiple drugs. Recent meta-analysis for VA-induced pleural effusion (1970–2020) by Tryfon *et al*.[9] concluded that only 28 cases could be attributed to VA solely. Out of these 28 cases, 17 (60.7%) had exudative EPE with simultaneous eosinophilia only in 10 cases. Evidence so far has revealed no temporal relationship between the initiation of VA and the occurrence of event. Some cases have occurred within days of the initiation of drug treatment, while others may not manifest until several years of treatment, like our case. However, withdrawal of the drug led to resolution in most of the cases.[4,8,9] The potential causative mechanism remains elusive too. Several theories are postulated, including direct drug toxicity, hypersensitivity reactions and oxidant-induced mesothelial damage.[4,5] Elevated levels of interleukin 3,5 and granulocyte monocyte colony stimulating factor have been linked to prolonged survival of eosinophils in pleural fluid.[5] Given the scanty scientific evidence and heterogeneity of VA-induced pleural reactions, the possibility of underreporting can't be overlooked. If the clinician manages to confirm the diagnosis correctly, treatment is simple; discontinuation of the drug.

EPE is commonly defined as pleural fluid with ≥10% eosinophils. EPE is estimated to affect 5–16% of people and

is caused by a variety of conditions including infectious diseases, chest trauma, malignancies, autoimmune diseases, exposure to asbestos, drug reactions, and pulmonary embolism.[1,10] Retrospective analysis by Krenke *et al*.[10] showed that malignancy (34.8%) and infectious diseases (19.2%) were the leading causes of EPE. Oba *et al*.[3] reported malignancy as the most common cause of EPE. However, no significant correlation was found between the eosinophil count in pleural fluid with that in blood or any other laboratory parameters. Also, at 40% cut off, pleural fluid eosinophilia could not differentiate malignant from non-malignant causes (sensitivity 85%, specificity 34.3%)[10] There is limited data on drugs inducing EPE, which include dantrolene, nitrofurantoin, fluoxetine, isotretinoin, angiotensin converting enzyme inhibitors, isoniazid, phenytoin, clozapine, propylthiouracil, and gliclazide.

Drug-induced reaction is a diagnosis of exclusion. It requires meticulous history-taking and extensive evaluation. Several widely available cost-effective tests may be used to rule out alternative causes like: pleural fluid cytology and tumour markers like carcinoembryonic antigen for malignant aetiology, parasite/parasite eggs on stools or pleural fluid along with parasite-specific serology for parasitic infections, sputum for acid fast bacilli/GeneXpert, and tuberculin skin test for tuberculosis, pleural fluid pyogenic culture and several other laboratory parameters for para-pneumonic effusions, blood eosinophil count and other organ-specific tests for hyper-eosinophilic syndrome etc.[4,10,11] A quick approach to drug-induced EPE is briefly discussed in Figure 2. Once alternative causes are rigorously excluded, the Naranjo probability scale can be used to assess the likelihood that an event is related to a drug. It is a set of 10 weighted questions on factors like drug levels, dose–response relationships, previous exposure to drugs, temporal association of drugs and events etc. A score of ≥9 reflects definite association. Our case had a score of 7, which fell into the probable category on the Naranjo scale. This scale is not valid in the case of drug-drug interactions.[6] Our patient

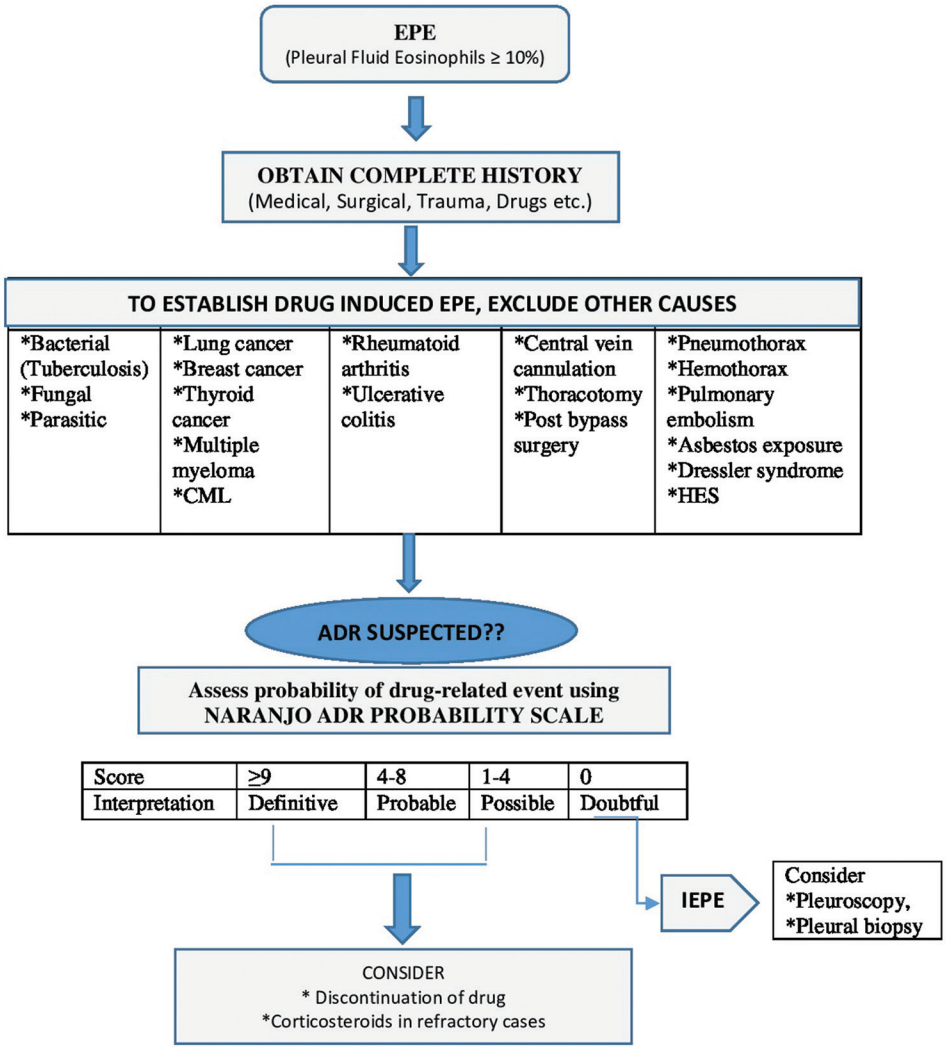

Figure 2: Stepwise approach to drug-induced eosinophilic pleural effusion flowchart.[1,5,10] EPE: Eosinophilic pleural effusion, CML: Chronic myeloid leukaemia, ADR: Adverse drug reaction, HES: Hyper-eosinophilic syndrome, IEPE: Idiopathic eosinophilic pleural effusion

was not on any medications other than VA. The drug was not re-administered in view of ethical concerns. For affordability reasons, serum levels of drug could not be monitored. Moreover, evidence suggests that therapeutic drug monitoring has a limited role in VA toxicity.[7]

VA-induced EPE is a rare occurrence and difficult to prove, but treatment is relatively simple. In most cases, such as ours, discontinuing the drug is sufficient, but corticosteroids may be required in some cases.[4,9] Limited scientific evidence and uncertain pathogenesis impede the development of diagnostic algorithms. A systematic approach can help evade costly invasive testing and procedures especially in resource-constrained countries.

CONCLUSION

VA is widely used by clinicians for a variety of disorders. It is a rare cause of EPE. Clinician should be aware of such a possibility and should not miss drug history especially in undiagnosed cases of pleural effusion. High degree of suspicion and systematic approach is imperative to clinch a correct diagnosis, thereby saving time and money.

Acknowledgements
Special thanks to Dr. Anita Both, Department of Pathology and Dr. Ramesh Guleria, Department of Microbiology, Shri Lal Bahadur Shastri Medical College & Hospital for their cooperation.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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