LETTERS TO THE EDITOR

Valproic acid-induced eosinophilic pleural effusion: A case report and brief review

ANNALS OF CLINICAL PSYCHIATRY 2020;32(4):288-290 doi: 10.12788/acp.0004

Gus Zhang, MD

TO THE EDITOR:

Valproic acid (VPA) is commonly used for mood stabilization, seizure prevention, and migraine headache prophylaxis. It has a wide therapeutic index and few adverse effects, including nausea, tremor, and sedation. Rarely, pancreatitis and hepatotoxicity may occur.

Eosinophilic pleural effusion (EPE) is a pleural effusion that contains ≥10% eosinophil content.[1] Etiologies include malignancy, trauma, pneumothorax, infection, autoimmune disorders, pulmonary embolism, congestive heart failure, drug reaction, and idiopathic causes. It can occur as a rare but serious adverse reaction to VPA therapy. Although VPA has been in widespread clinical use for decades, VPA-induced EPE is relatively unknown in psychiatric literature. The diagnosis of VPA-induced EPE can be made only after other etiologies of EPE are excluded. There is no specific treatment, except discontinuation of VPA. Here I present a case of suspected VPA-induced EPE.

Case report

Mr. D, a 68-year-old African American male with a history of Alzheimer's dementia, was admitted to a medical ward for agitation, weight loss, weakness, anemia, and decreased appetite. His medications included benztropine, quetiapine, memantine, mirtazapine, and VPA. He had been receiving VPA, 500 mg/d, for the past 5 months. On admission, chest radiograph and CT revealed a left pleural effusion of unknown etiology. Left thoracentesis removed 350 ml of exudative fluid that had a pH level of 7.7, lactate dehydrogenase (LDH) 676 U/L, protein 3 g/dL, erythrocyte 12,000/mL, and leukocyte 6,190/mL, with 30% eosinophils. There were no bacteria growth or malignant cells.

Three days later, repeat CT showed diminished original left effusion, but interval development of a large right effusion. Right thoracentesis removed 960 mL of exudative fluid that had a pH level of 7.96, LDH 1,783 U/L, protein 4 g/dL, erythrocyte 9,000/mL, and leukocyte 1,629/mL, with 26% eosinophils. At this point, VPA-induced EPE was suspected and VPA was discontinued. Three days later, radiography showed resolution of bilateral effusions. Repeat radiography 20, 29, and 53 days later showed no recurrence.

DISCUSSION

A PubMed search reveals 16 reports of EPE associated with VPA, including 1 pediatric case (**TABLE**).[2-17] Only 1 report was published before 2000,[11] which suggests little awareness of this phenomenon until recently. Most of the reports were not published in the psychiatric literature. The lowest reported dose of VPA was 250 mg/d.[5] Five cases had bilateral effusions,[2,4,7,12,14] and 2 cases developed pericardial effusion.[15,16] Where published, pleural fluid eosinophil content always exceeded serum eosinophil content. Antibiotic or corticosteroid medications were used in 2 cases each.[4,7,12,13] Resolution of effusion followed discontinuation of VPA in all cases, but time to resolution ranged from 3 days to 6 months.

A limitation of this case report is that all alternative causes of EPE cannot be exhaustively eliminated, nor can resolution of effusion be definitively attributed to cessation of VPA treatment. This case is unique due to Mr. D's continued effusion after thoracentesis and the development of a second effusion in the opposite pleural cavity while he was still being treated with VPA. This implicates VPA as the cause and shows that stopping VPA was a necessary intervention.

In summary, clinicians should be aware of VPA-induced EPE and, if suspected, discontinue VPA promptly. Valproic acid-induced EPE is increasingly reported in the literature, but much remains unknown, including the incidence, causative mechanism, risk factors, and preventative measures. There also are no guidelines for rechallenge with VPA. These issues warrant clinical vigilance and further research. ■

DISCLOSURE: The author reports no financial relationships with any companies whose products are mentioned in this article, or with manufacturers of competing products.

TABLE
Case reports of valproic acid–induced eosinophilic pleural effusion

		VPA use		Pleural effusion characteristics				
Case report	Age, sex	Dose (mg/d)	Therapy duration	Location	Eosinophil %[a]	Time to resolution	Serum eosinophil %	Additional interventions
Abdelhamid[2]	56 M	1,000	5 days	Bilateral	39	1 month	NR	NR
André[3]	57 F	1,000	NR	Left	NR	6 months	NR	NR
Aral[4]	15 F	750	4 weeks	Bilateral	10	5 days	1.9	Methylprednisolone
Bullington[5]	25 M	250	NR	Right	75	1 month	12	NR
Catalán[6]	19 F	1,000	2 months	Right	51	6 months	NR	NR
Chiles[7]	34 M	1,500	2 weeks	Bilateral	40	"Several days"	15.4	Gatifloxacin
Fernández-Pérez[8]	64 F	1,500	2 months	Left	35	4 months	NR	NR
Joshi[9]	48 F	1,500	NR	Right	44	6 months	12	NR
Kamenetsky[10]	30 M	1,000	2 weeks	Right	48	"A few days"	6.6	NR
Kaufman[11]	42 M	1,000	9 months	Left	62, 82	"Several days"	26	NR
Kravetz[12]	34 M	1,500	2 weeks	Bilateral	40	13 days	NR	Vancomycin and ceftazidime
Savvas[13]	44 F	NR	20 days	Right	40	2 weeks	12	Methylprednisolone
Shaib[14]	38 M	NR	NR	Bilateral	45, 67	10 weeks	NR	NR
Taser[15]	42 F	1,250	6 years	Left and pericardial	NR	3 months	NR	NR
Tonnelier[16]	50 F	1,500	1 month	Right and pericardial	65	6 weeks	NR	NR
Tryfon[17]	70 M	500	4 months	Right	NR	15 days	NR	NR
Case described in this article	68 M	500	5 months	Bilateral	30, 26	3 days	3.2	NR

[a]>1 value indicates multiple thoracenteses were performed.

F: female; M: male; NR: not reported; VPA: valproic acid.

REFERENCES

1. Adelman M, Albelda SM, Gottlieb J, et al. Diagnostic utility of pleural fluid eosinophilia. Am J Med. 1984;77:915-920.
2. Abdelhamid MS, Percival M, Sivakumaran P. Sodium valproate - a rare cause of eosinophilic pleural effusion. Intern Med J. 2011;41:802-803.
3. André S, Drowart A, De Bels D. Lymphocytic pleural effusion associated with valproic acid. Eur J Intern Med. 2005;16:535.
4. Aral A, Usta MB, Karabekiroglu K. Valproic acid-induced eosinophilic pleural effusion in a patient with pediatric bipolar disorder. Asia Pac Psychiatry. 2017;9. doi: 10.1111/appy.12276.
5. Bullington W, Sahn SA, Judson MA. Valproic acid-induced eosinophilic pleural effusion: a case report and review of the literature. Am J Med Sci. 2007;333:290-292.
6. Catalán Alcántara A, Sánchez Pérez M, del Campo MD, et al. Eosinophilic pleural effusion secondary to treatment with valproic acid. Actas Esp Psiquiatr. 2005;33:401-402.
7. Chiles C, van Wattum PJ. Pleural fluid eosinophilia with combined pharmacotherapy. Psychosomatics. 2003;44:436-437.
8. Fernández-Pérez R, Manuel Alvarez-Dobaño J, Suárez-Antelo J, et al. Eosinophilic pleural effusion associated with the addition of sodium valproate. J Clin Psychopharmacol. 2009;29:310-311.
9. Joshi P, Kasmani R, Hollingsworth J, et al. Divalproex sodium-induced eosinophilic pleural effusion. Am J Ther. 2009;16:593-595.
10. Kamenetsky Z, Da'as N, Esayag Y, et al. Valproic acid-induced eosinophilic pleural effusion: a case report and review of the literature. Neurologist. 2012;18:39-40.
11. Kaufman J, O'Shaughnessy IM. Eosinophilic pleural effusion associated with valproic acid administration. South Med J. 1995;88:881-882.
12. Kravetz JD, Federman DG. Valproic acid-induced eosinophilic pleural effusion. South Med J. 2003;96:803-806.
13. Savvas SP, Dimopoulou E, Koskinas J. Valproic acid-associated eosinophilic pleural effusion treated with corticosteroids. Eur J Intern Med. 2006;17:71.
14. Shaib FH, Patel B. A case of eosinophilic pleural

LETTERS TO THE EDITOR

effusion secondary to valproic acid. Chest. 2000;118:308S.
15. Taşer N, Sarikaya M. An unusual case of pleuropericardial neutrophilic effusion associated with valproate. J Formos Med Assoc. 2015;114:375-376.
16. Tonnelier JM, Mocquard Y, Broch C, et al. Febrile pleuropericarditis during valproic acid treatment [in French]. Presse Med. 2001;30:62-63.
17. Tryfon S, Saroglou M, Kazanas K, et al. Sodium valproate as a cause of recurrent transudative pleural effusion: a case report. J Med Case Rep. 2009;3:51.

Gus Zhang, MD
Department of Psychiatry
The University of Texas Southwestern
Medical Center
Dallas, Texas, USA

CORRESPONDENCE: Gus Zhang, MD, Department of Psychiatry, The University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390, USA. **E-MAIL:** gus.zhang@utsouthwestern.edu