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Literature Review with Illustrative Case

Eosinophilic Pleural Effusion Induced by Paliperidone Palmitate: Case Report and Literature Review

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Background: *Eosinophilic pleural effusions are defined by an eosinophil count ≥ 10% in pleural fluid and represent approximately 10% of exudative pleural effusions. They are associated with a large spectrum of etiologies, both benign and malignant. Drug-induced eosinophilic pleural effusions remain rarely described.* **Objective and Methods:** *After ruling out other causes with a careful diagnostic assessment, we retain paliperidone as the etiology, given the disappearance of the pleural effusion after drug discontinuation.* **Results:** *We report the first case of eosinophilic pleural effusion induced by paliperidone palmitate treatment.* **Conclusion:** *After considering other etiologies, drug-induced eosinophilic pleural effusion should be sought.*

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Key words: eosinophilic pleural effusion, paliperidone palmitate, iatrogenic pleural effusion, drug-induced eosinophilic pleural effusion, case report.

INTRODUCTION

Eosinophilic pleural effusions (EPEs), first described by Harmsen in 1894, are defined as pleural fluids with at least 10% eosinophils in the nucleated cell count and represent approximately 10% of exudative pleural effusions.[1–6] EPEs are associated with a broad spectrum of benign and malignant etiologies that correlate with prevalent diseases in the population.[2,3] It therefore requires a careful diagnostic process. Drug-induced EPEs still remain rarely described and are mainly caused by cardiovascular or neuropsychiatric medicines.[5]

Paliperidone palmitate is an atypical antipsychotic used in schizophrenia. Injection-site pain, insomnia, increased weight, akathisia, and anxiety are the most listed adverse events. Upper respiratory tract infections, pulmonary hypertension, and thromboembolism have been previously described as pulmonary side effects.[7] Here we report the first case of EPE caused by paliperidone palmitate treatment, proven by its disappearance after discontinuation of the drug.

ILLUSTRATIVE CASE

We describe the case of a 38-year-old Belgian Caucasian woman presenting with abrupt, left laterothoracic pain, dependent on breathing, associated with asthenia and exertional dyspnea. She reported no history of trauma. The patient had no fever, no cough, no abdominal complaints, and no diarrhea.

Her medical history included hypothyroidism secondary to total thyroidectomy for benign multinodular colloidal goiter, cesarean section pregnancy, and schizophrenia. Breast cancer was found in both maternal and paternal great aunts. She was an active

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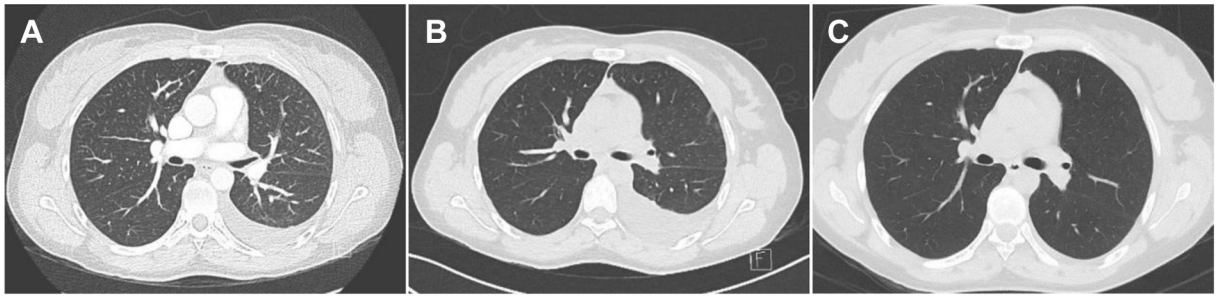
FIGURE 1. ***A*: Chest computed tomography (CT) angiography showing left pleural effusion. No pulmonary embolism or parenchymal abnormalities. Infracentimetric mediastinal lymph nodes. *B*: Increased pleural effusion 10 days after pleural puncture. *C*: Disappearance of the left pleural effusion on the follow-up chest CT 2 months after stopping paliperidone palmitate.**



smoker (20 pack-year units). She had a former methamphetamine addiction that began at age 16 and ended last year. Her drug use was recreational, with an average of 1 gram snorted every 2 weeks with a maximum of 1 gram snorted every 5 days. She has had 3 extended psychiatric hospitalization episodes in the last 10 years. She lived in Belgium with no history of travel. There was no significant asbestos exposure or recent respiratory infection.

Her treatment included levothyroxine (L-Thyroxine; Orifarm Healthcare, Odense, Denmark) 125 µg once a day and paliperidone palmitate (Xeplion; Janssen-Cilag, Olen, Belgium) given by monthly intramuscular injection, which was introduced 3 months earlier: first injection of 75 mg, then a second of 125 mg 1 week later, followed by a monthly injection of 150 mg.

Physical examination showed a pleural syndrome at the left base. Cardiac, abdominal, and skin physical examinations were unremarkable.

Biology highlighted a moderate inflammatory syndrome C-reactive protein at 48 mg/L (standard <10 mg/L) without hyperleukocytosis, a mild eosinophilia at 980/mm^3 (standard 600/mm^3), normal thyroid results, and an increased D-dimers to 2.76 mg/L (standard <0.5 mg/L).

Toxicological analyzes in the blood (ethanol, benzodiazepines, barbiturates, amphetamine) and urine (amphetamine, methamphetamine, cocaine, morphine, and cannabis) were negative.

Chest computed tomography angiography showed no pulmonary embolism (Figure 1A), but there was a moderate left pleural effusion without pneumothorax or parenchymal abnormality.

The pleural puncture revealed 700 mL of cloudy yellowish fluid with cytological analysis consistent with eosinophilic exudate (58% eosinophils, absolute eosinophil count 4538/mm^3, ratio of pleural proteins/plasma proteins 0.63, and pleural lactate dehydrogenase 781 U/L). pH Level was 7.2, and direct examination of the pleural fluid did not detect any parasites, mycobacteria, and fungi. The bacterial, mycobacterial, and fungal cultures remained negative. Cytological analysis did not find any malignant cells.

The immune assessment was normal (antinuclear factor, antineutrophil cytoplasmic antibodies and anticyclic citrullinated peptide antibodies, serum protein electrophoresis and immunoglobulin assay).

We did not perform parasitological examination of stools.

The bronchial fibroscopy showed no endobronchial lesion. The bronchoalveolar lavage was unremarkable. Despite our puncture, the left pleural effusion progressed on the chest computed tomography scan performed 10 days after the procedure (Figure 1B).

Pleural biopsies were taken thoracoscopically. Histologic analyses were in favor of nonspecific reactive inflammatory pleurisy with no evidence of malignant cells or sign of tuberculosis.

In the absence of an alternative diagnosis, we suspected a drug origin.

In our patient, discontinuation of paliperidone palmitate resulted in resolution of the symptoms, normalization of the biology, and disappearance of the left pleural effusion on the 2-month follow-up chest computed tomography scan (Figure 1C), arguing in favor of drug toxicity due to paliperidone palmitate.

DISCUSSION

EPEs are relatively rare conditions, accounting for nearly 10% of pleural exudates.[1–5] Their causes are

TABLE 1. Causes of Pleural Fluid Eosinophilia

Exudative effusions	
Drugs	Please refer to Table 2
Idiopathic	
Infection	Bacteria (e.g., parapneumonic effusion)
	Fungi (e.g., *Histoplasma capsulatum*, *Coccidioides immitis*)
	Mycobacteria
	Parasites (e.g., amebiasis, *Ascaria*, *Dracunculus*, echinococcosis, filaria, *Paragonimus*, *Strongyloides*, *Toxocara*)
	Virus
Inflammatory	Acute eosinophilic pneumonia
	Chronic eosinophilic pneumonia
	Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)
	Rheumatoid effusion
Malignancy	Lymphoma
	Mesothelioma
	Metastatic carcinoma
Pulmonary embolism	
Toxin	Benign asbestos effusion
Trauma	Hemothorax
	Pneumothorax
	Thoracentesis
	Thoracic surgery
	Thoracoscopy
Transudative effusions	
Cirrhosis	
Heart failure	

According to the UpToDate website www.uptodate.com

numerous. The spectrum of diseases associated with EPE mirrors that of pleural effusions in general and is strongly affected by the prevalent diseases in the study population[2–4] (Table 1).[8] EPEs have long been associated with benign processes, but more recent reports have shown that eosinophilic effusions are as likely as noneosinophilic effusions to be associated with malignancies.[2,3,6]

Drug-induced pleural diseases should be suspected after ruling out other possibilities. They are less well known to clinicians than drug-induced parenchymal lung diseases. They are rarely described and are most often the subject of case reports.[4,5,9] There are currently approximatively 35 drugs that can cause EPE (Table 2),[10] mainly cardiologic or neuropsychiatric medications.

Despite careful evaluation, the cause of EPE often remains unknown, as shown in a meta-analysis of 687 cases in which the most common causes of EPE were malignancies (26%) followed by idiopathic (25%) and parapneumonic (13%) effusions.[2,4]

The development of EPE results from increased eosinophil production in the bone marrow, migration of these cells into the circulation, adhesion to the endothelium, migration across endothelial barriers to tissues, and prolonged survival of these eosinophils at the site of inflammation. This process is in response to stimulation by cytokines and chemokines such as eotaxin, interleukin-3, interleukin-5, granulocyte-monocyte cell-stimulating factor, and regulated on activation, normal T-cell expressed and secreted.[11–14] Peripheral eosinophilia may be associated with EPE in 25%–75% of cases.[12,15] When peripheral eosinophilia does occur, it usually follows EPE and disappears after the pleural eosinophilia resolves.[12]

The diversity of etiological factors of EPE suggests the presence of different pathogenic mechanisms. EPE occurs within hours of a spontaneous pneumothorax, within 10–14 days of a hemothorax, whereas it is unpredictable in drug-induced EPE. It most often occurs within months from first drug exposure, with a wide range from a few days to years.[9,12,14,15]

As a fact, EPEs resulting from mechanical pleural injury do not seem to be caused by a Th-2-mediated mechanism, whereas nitrofurantoin- or parasite-induced

TABLE 2. Drugs Associated With Eosinophilic Pleural Effusions

Antimicrobials	Antibacterial drugs	Nitrofurantoin
	Antituberculosis drugs	Isoniazid
	Antiviral drugs	Acyclovir
Cardiovascular agents	Angiotensin-converting enzyme inhibitors	Lisinopril
		Imidapril
		Perindopril
		Cilazapril
	Antithrombotics	Warfarin
	Beta blockers	Acebutolol
	Calcium antagonists	Diltiazem
	Statins	Simvastatin
		Pravastatin
Neuropsychiatric agents	Anticonvulsants	Valproic acid
	Antidepressants	Trimipramine
		Fluoxetine
	Antiparkinsonians	Bromocriptine
	Atypical antipsychotics	Clozapine
		Olanzapine
	Myorelaxants	Dantrolene
		Tizanidine
Oncologic agents	Alkylating agents	Cyclophosphamide
	Antimetabolites	Methotrexate
Others	Antiacnes	Isotretinoin
	Antithyroids	Propylthiouracil
		Methimazole
		Carbimazole
	Intestinal anti-inflammatory drugs	Mesalazine
		Sulfasalazine
	Sulfonylureas	Gliclazide
	TNF-α inhibitors	Infliximab
	Various	Cyanoacrylate
		Crack cocaine
		Implantable cardiac devices
		Radiation therapy
		Vitamine B5/H

According to the Pneumotox website www.pneumotox.com.
TNF-α = tumor necrosis factor α.

EPEs have a clinical course suggestive of a Th-2 hypersensitivity reaction.[9,14,15]

Although the exact pathogenic process is not yet clearly elucidated, our knowledge of the mechanisms of cell recruitment in the pleura is rapidly advancing. As shown in a 2002 study, normal human pleural mesothelial cells can produce several eosinophil-active chemokines, in particular, eotaxin and regulated on activation, normal T-cell expressed and secreted, through different *in vitro* signaling pathways, depending on Th-1 (interferon-γ) and Th-2 (interleukin-4) immune responses, both of which act synergistically with tumor necrosis factor α.[13] Infiltrating T-helper lymphocytes thus appear to be key players in the regulation of chemokine production.[13] This also suggests that pleural mesothelial cells play an active role in the recruitment of inflammatory cells to the pleural space in response to signals within the pleural microenvironment.[13,16] Could the explanation for the pathogenesis of drug-induced EPE thus be a Th-2 hypersensitivity reaction?

Symptoms of drug-induced EPE usually begin to improve within the first few days after stopping the drug, and pleural effusion completely resolves within several months.[8] Treatment with oral glucocorticoids has been reported to accelerate resolution in a few case reports.[17,18]

The literature does not comment on the possibility of reintroducing the causal drug of EPE. However, case reports have shown recurrences of EPE when the offending drug is reintroduced.[17,19] These recurrences are again treated by drug discontinuation, and the addition of corticosteroids is sometimes necessary.[17] The situation should therefore be assessed on a case-by-case basis.

In our case of EPE, we performed a broad etiological workup. Malignant tumours (bronchial carcinoma, pleural metastasis, mesothelioma, hematological malignancy) and infectious diseases (tuberculosis, empyema, or parapneumonic pleurisy) are frequent causes of EPE[4] (Table 1).[8] Cytological and microbiological analysis of pleural fluid and bronchoalveolar lavage as well as histological analysis of pleural biopsies have refuted these diagnostic hypothesis altough 2 years of follow-up are required to definitively exclude pleural malignancy.

The patient had no significant exposure to asbestos, no history of travel, and no abdominal complaints that might have pointed to a benign asbestos effusion or parasitic etiology.

An EPE secondary to amphetamine use was considered at first in this case. Literature reported cases of methamphetamine-induced lung injury including pulmonary edema, pneumonitis, acute respiratory distress syndrome, alveolar hemorrhage, and pulmonary hypertension but no cases of EPE.[20,21] We finally withdrew this hypothesis because the patient had not been using drugs for a year (proved by blood and urine toxicology tests).

Other etiologies such as pulmonary embolism, pneumothorax, hemothorax, and autoimmune conditions including rheumatoid arthritis were considered but ruled out by chest computed tomography angiography and laboratory tests.

As seen in a 2003 study, repeated thoracentesis does not appear to be a risk factor for EPE per se, but the available data are still conflicting.[22]

In the absence of an alternative diagnosis, we suspected drug-induced EPE. We finally opted for paliperidone palmitate in view of the biological, clinical, and radiological resolution after discontinuation of the drug.

According to Naranjo's Adverse Drug Reaction Probability Scale, our case of EPE should be considered as a probable side effect induced by paliperidone palmitate.[23] The onset after drug administration (+2), resolution after drug discontinuation (+1), lack of other explanation (+2), and confirmation of the adverse reaction by objective evidence (+1) give a total score of 6. The lack of information prevented us from having a higher score to confirm our hypothesis. Indeed, to date, no one has described this side effect induced by paliperidone palmitate in the literature. Also, it is not known whether this side effect is dose dependent. Finally, for ethical reasons, we did not readminister the drug to the patient to study the recurrence of the EPE.

Paliperidone palmitate (Xeplion; Janssen-Cilag) is the long-acting injectable form of paliperidone. This palmitate ester is one of the atypical antipsychotics indicated for the acute and maintenance treatment of schizophrenia in adult patients.[24,25] It is used in schizophrenia patients who have previously responded to oral risperidone or its active metabolite, 9-hydroxy risperidone (paliperidone). The paliperidone palmitate research in demonstrating effectiveness randomized trial, designed to reflect real-world management of schizophrenia, demonstrated the superiority of monthly intramuscular injection of paliperidone palmitate over daily oral antipsychotics in increasing adherence to treatment and delaying treatment failure.[7,24]

Pharmacokinetically, paliperidone strongly inhibits serotonin 5-hydroxytryptamine 2A and dopamine D2 receptors. It also antagonizes α1 adrenergic receptors and, to a lesser extent, histamine H1 and α2 adrenergic receptors.[25] The most commonly reported side effects of paliperidone palmitate are injection-site pain, insomnia, weight gain, akathisia, and anxiety.[7] Upper respiratory tract infections, pulmonary hypertension, and thromboembolism have been previously described as pulmonary side effects.[7]

CONCLUSION

EPEs are uncommon conditions but require a careful diagnostic approach with a priority search for malignancies, infectious diseases, or traumatic causes. The differential diagnosis is wide, and a large proportion of idiopathic EPEs remain even after careful evaluation. After considering other etiologies, a drug-induced pleural disease should be sought. We believe that with the introduction of new drugs, the number of drugs implicated in pleuropulmonary toxicity will continue to increase. In our patient, discontinuation of paliperidone palmitate (Xeplion; Janssen-Cilag) led to a favorable clinical course,

improvement of symptoms, normalization of biology, and disappearance of the left pleural effusion at 2 months. We therefore believe that paliperidone palmitate is the cause of our patient's eosinophilic pleurisy, which would be the first case ever described worldwide.

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SUPPLEMENTARY DATA

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