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CASE REPORT

Eosinophilic Exudative Pleural Effusion After Initiation of Tizanidine Treatment: A Case Report

Ghassan Moufarrege, MD,* Evan Frank, MD, PhD,* and Donna D. Carstens, MD†

*Department of Anesthesiology and †Asthma, Allergy and Pulmonary Associates, Thomas Jefferson University, Philadelphia, Pennsylvania

ABSTRACT

In this case report, we present a 42-year-old man with history of chronic low back pain after a work-related injury. The patient failed multiple therapeutic modalities both conservative and interventional, including numerous spinal injections and placement of a spinal cord stimulator. Finally, an intrathecal morphine pump was placed to control his pain in addition to oral pain medications. The course of the treatment included adding a muscle relaxant, tizanidine (Zanaflex®), to control spasms in the lower extremities. Six weeks after starting tizanidine, a large pleural effusion was noted incidentally on a computerized tomography scan of the thoracic and lumbar spine. The patient underwent work-up for the pleural effusion; all tests came back negative. Finally, a drug reaction to tizanidine was suspected. The drug was discontinued, and 4 weeks later the pleural effusion resolved.

Key Words. Eosinophilic Exudative Pleural Effusion; Tizanidine; Antinociceptive Properties; α2-Receptor Agonist

Introduction

Tizanidine (Zanaflex®, Athena Neurosciences, San Francisco, Calif) is an α2–adrenergic-receptor agonist commonly used in patients with chronic pain due to muscle spasms. It is also used for spasticity associated with central nervous system disorders, such as multiple sclerosis. The mechanism of action is related to its skeletal muscle relaxant and antinociceptive properties. Tizanidine has been reported to relieve neuropathic-type pain, such as the pain associated with complex regional pain syndrome, trigeminal neuralgia, and post-herpetic neuralgia [1]. As an α2-receptor agonist, tizanidine is similar to clonidine and other α2-receptor agonists in structure; however, tizanidine has one tenth to one fiftieth the antihypertensive potency of clonidine [1–3]. When compared with baclofen, tizanidine is as effective as an antispasticity agent; however, tizanidine has fewer side effects, mainly less muscle weakness, than baclofen [4].

Common adverse reactions include asthenia (weakness, fatigue, and/or tiredness), somnolence, sedation, dizziness, dry mouth, increased spasms or tone, hypotension, and bradycardia [1,3]. Other, less common side effects include urinary tract infection, constipation, liver injury with abnormal liver function tests, vomiting, speech disorder, blurred vision, urinary frequency, flu syndrome, dyskinesia, nervousness, pharyngitis, and rhinitis [3]. After conducting a literature search with PubMed, we found no prior report of tizanidine causing pleural effusion. We report here a case of a patient who developed eosinophilic exudative pleural effusion after initiation of tizanidine treatment.

Case Report

The patient is a 42-year-old white man with a long history of severe low back pain and bilateral lower

Reprint requests to: Evan Frank, MD, PhD, Thomas Jefferson University, Department of Anesthesiology, Jefferson Pain Center, 834 Chestnut Street, Suite T-150, Philadelphia, PA 19107. Tel: (215) 955-7246; Fax: (215) 923-5086; E-mail: Evan.Frank@mail.tju.edu.

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extremity pain after a work-related injury in 1980. He was diagnosed with a herniated disc and underwent three laminectomies, and finally, fusion at L4-L5 and L5-S1 without relief of his pain. In between the surgeries, he had numerous spinal injections without benefit. He was diagnosed with post-laminectomy syndrome and had a spinal cord stimulator implanted in 1998, which failed to control his pain. Finally, the patient had an intrathecal pump implanted in January 2000. The surgical placements of both the spinal cord stimulator and the intrathecal pump were uncomplicated and without development of traumatic hemothorax. The initial pump medications and dosages were morphine 3 mg/day and bupivacaine 1.8 mg/day. Over time, the patient required multiple gradual adjustments in his pump medications and dosages including the addition of clonidine on August 11, 2000. The latest intrathecal pump medication dosages, in November 2001, were: morphine 30 mg/day, bupivacaine 12 mg/day, and clonidine 900 µg/day. Between August 2000 and November 2001, all three medications (morphine, bupivacaine, and clonidine) were delivered continuously through the pump without interruption. In addition, the patient was on chronic oral pain medications, as shown in Table 1. The patient had allergies to aspirin, ketorolac tromethamine, propoxyphene napsylate/acetaminophen, and intravenous dye.

On November 10, 2000, baclofen was added to his medications due to increasing cramps in the lower extremities. However, the patient developed nausea, vomiting, and diarrhea as side effects. On November 17, 2000, baclofen was discontinued, and tizanidine was added instead at a dose of 2 mg orally every 8 hours. Six weeks later, on January 3, 2001, a large right-sided pleural effusion was noted incidentally on a computerized tomography (CT) scan of his thoracic and lumber spine that was done after a myelogram as part of further assessment of his low back pain. In February 2001, the dose of tizanidine was increased to 4 mg orally every 8 hours. Later on in February 2001, the patient complained of shortness of breath, dyspnea on exertion, and pleuritic chest pain, but no cough, sputum production, fever, or chills; therefore, the pulmonary service was consulted and became involved in the care of the patient.

Three weeks later, a chest x-ray showed worsening of the pleural effusion on the right; otherwise, no infiltrates or nodules were noted. The pleural effusion was tapped and was found to be exudative. On physical examination, the patient

Table 1 Oral and transcutaneous medications, CXR findings, CT scan of chest findings, and findings from auscultation and percussion at right lower lobe of the lung (RLL) from the time before tizanidine was introduced until resolution of pleural effusion

	Feb-00	Apr-00	Oct-00	Nov-00	Nov-00	Jan-01	Feb-01	Mar-01	Apr-01	Jul-01	Aug-01	Sep-01	Oct-01	Nov-01
Fentanyl patch (µg/hr)	25	25	25	25	25	50	100	100	100	100	100	100	100	100
Morphine sulfate 30 mg (tabs/month)		150	150	150	150	150	150	150	150	150	150	150	150	150
Oxycodone elixir 20 mg/mL (mL/month)								30	90	90	90	90	90	90
Gabapentin (mg q 8 hr)	900	900	900	900	900	900	900	900	1200	1200	1200	1200	1200	1200
Fluoxetine (mg q a.m.)								20	20	20	20	20	20	20
Tizanidine (mg q 8 hr)				2	2	2	4	4	4	4	D/C			
Baclofen (mg q 8 hr)				5	D/C									
Pleural effusion on CXR							P	P	P	P	P	N/A	N/A	A
Pleural effusion on CT scan						P								
Breath sounds at RLL						A	A	A	A	A	A	P	P	P
Dullness to percussion at RLL						P	P	P	P	P	P	A	A	A

Abbreviations: D/C = discontinued; P = present; A = absent; N/A = not available.

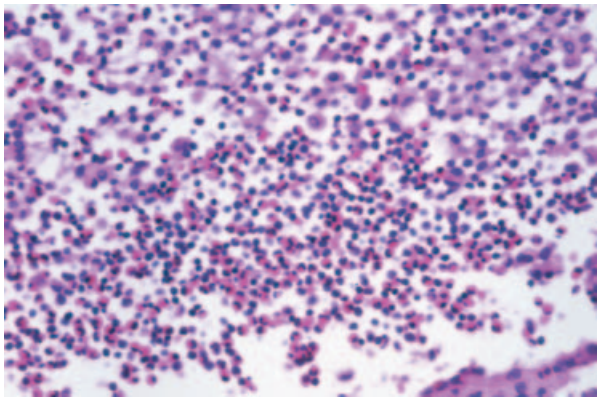

Figure 1 Cytology slide of the pleural fluid showing the eosinophils (the cells with pinkish cytoplasm).

had stable vital signs and no fever. His lung exam revealed absent breath sounds over the right lower lung lobe and dullness to percussion. The rest of the physical exam was unremarkable. On March 20, 2001, the patient was admitted to the hospital for a malignancy work-up and to rule out pulmonary embolism. The patient had an ultrasound-guided thoracentesis; 600 ml of pleural fluid was tapped. The pleural effusion was sent to Cytology and proved to be again exudative with eosinophils constituting 10% of the white blood count (WBC) (Figure 1). Other pleural fluid characteristics, cell count, and chemistry are shown in Table 2. Cytopathology of the pleural fluid was negative for malignant cells. A ventilation perfusion scan of the

Table 2 Serum chemistry, complete blood count, pleural fluid characteristics, cell count, chemistry, PTT, and PT. Abbreviations: LDH = lactate dehydrogenase; Alk Phos = alkaline phosphatase; Ast = aspartate Aminotransferase; WBC = white blood count; RBC = red blood cell count; MCV = mean corpuscular volume; RDW = red cell distribution width; ANA = antinuclear antibodies; ANCA = antineutrophil cytoplasmic antibodies; C ANCA = cytoplasmic ANCA; P ANCA = perinuclear ANCA; X ANCA = atypical ANCA screen; RF = rheumatoid factor; PTT = partial thromboplastin time; PT = prothrombin time; INR = international normalization ratio; Abn = abnormal

Serum Chemistry

Test	Result	Normal Range	Units
Sodium	138	135–146	mmol/L
Potassium	3.9	3.5–5.0	mmol/L
Chloride	101	98–109	mmol/L
Co2	25	24–32	mmol/L
Anion Gap	12	4–16	mmol/L
Urea Nitrogen	9	10–26	mg/dL
Creatinine	0.8	0.7–1.4	mg/dL
Albumin	4.2	3.2–4.9	g/dL
Glucose	84	60–110	mg/dL
LDH	145	100–200	IU/L
Protein	6.8	6.0–8.5	g/dL
Calcium	9.9	8.5–10.5	mg/dL
Bilirubin, Total	0.8	0.2–1.2	mg/dL
Alk Phos	58	29–92	IU/L
Ast	24	7–42	IU/L

Pleural Fluid

Test	Result	Normal Range	*Units
Gross appearance	cloudy		
Supernatant	yellow		
RBC	427		M/L
WBC	2,731		M/L
Neutropil	26		%
Lymphocyte	21		%
Disintegrated WBC	3		%
Other	50		%
Glucose	117	60–110	mg/dL
LDH	235	100–200	IU/L
Protein	4.1	6.0–8.5	g/dL

* M = 10^6.

Complete Blood Count Serology

Test	Result	Normal Range	*Units
WBC	7.7	4–11	B/L
RBC	4.65	4.5–6.0	T/L
Hemoglobin	12.9	14.0–17	g/L
Hematocrit	38.9	42–52	%
MCV	84	80–94	fL
RDW	13.8	11.5–14.5	%
Platelets	169	140–400	B/L
Neutrophil	62.2	40–73	%
Lymphocyte	23.2	20–44	%
Monocyte	9.7	3–13	%
Eosinophil	4.5	0–6	%
Basophil	0.4	0–3	%
Abn Neutrophil	4.8	1.7–7.0	B/L
Abn Lymphocyte	1.8	1.0–4.0	B/L
Abn Monocyte	0.7	0.2–0.9	B/L
Abn Eosinophil	0.3	0–0.2	B/L

* B = 10^9; T = 10^{12}.

Serology

Test	Result	Normal Range	Units
ANA	negative		
C ANCA	negative		
P ANCA	negative		
X ANCA	negative		
RF	<20.0	0–30	IU/ml

Others

Test	Result	Normal Range	Units
PTT	29	24–42	sec
PT	14.6	11–15	sec
INR	1.12	0.77–1.15	

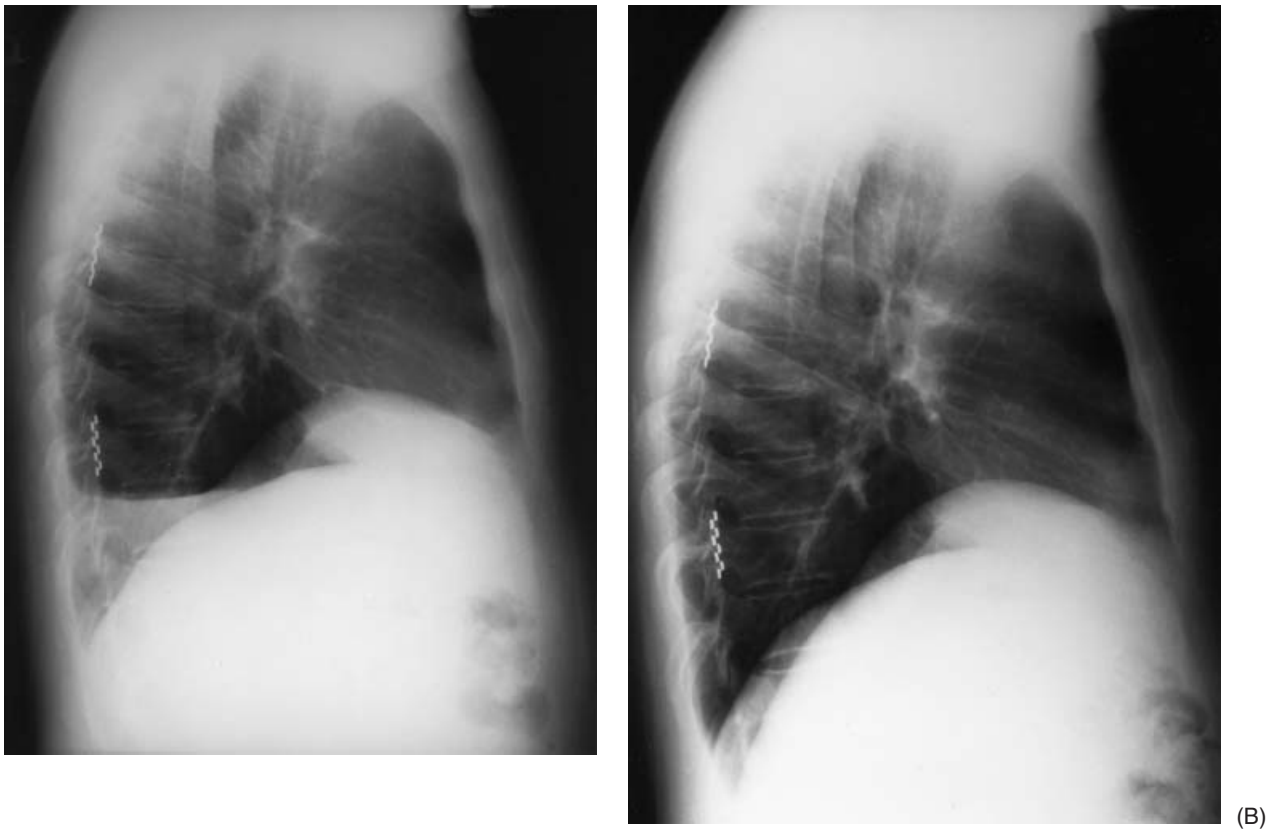

Figure 2 (A) Chest x-ray, lateral view. The arrow points to the pleural effusion. (B) Chest x-ray, lateral view after the resolution of the pleural effusion.

lung was negative for pulmonary embolism. A CT scan of the chest showed only the right pleural effusion. Other tests done include complete blood count, serum chemistry, connective tissue serology, liver function tests, prothrombin time, and partial thromboplastin time. The results of all these tests were unremarkable (Table 2). A pleural fluid gram smear was negative for organisms, and the culture revealed no growth in 3 days. Serum protein electrophoresis showed no abnormalities, and no monoclonal paraproteins were identified.

The patient was discharged 3 days later in stable condition and on the same pain medications mentioned previously in addition to albuterol sulfate and salmeterol xinafoate inhalers. He was followed on an outpatient basis.

The differential diagnosis of eosinophilic exudative pleural effusion includes drug reaction. In this case, the initiation of tizanidine correlated with the onset of pleural effusion, therefore, the provisional diagnosis for the cause of eosinophilic pleural effusion was drug reaction secondary to tizanidine. As a result, tizanidine was discontinued in August 2001. Four weeks later, upon a follow-up visit, the patient reported resolution of his symptoms. Chest physical exam showed clear breath sounds to auscultation and resonance to percussion at the right lower lobe. Chest x-rays (CXR) in November 2001 revealed resolution of the pleural effusion (Figure 2). Also, repeat pulmonary function tests showed significant improvement (Table 3).

Discussion

Pleural effusions are classified into transudative or exudative, to help determine etiologies in the differential diagnosis. A transudative pleural effusion indicates that there is a disturbance in the systemic factors that affect the production and the absorption of the pleural fluid. This results in a disturbance in the Starling forces across the capillary membranes in the pleura. This can be in the form of increased hydrostatic pressure (e.g., congestive heart failure) or decreased oncotic pressure (e.g., severe hypoalbuminemia), and results in the formation of low-protein content of the pleural fluid, called transudates. In this case, the capillary mem-

Table 3 Pulmonary function tests in July 2001 (during tizanidine treatment) and in October 2001(two months after tizanidine was discontinued)

	Jul-01			Oct-01			
Spirometry	Actual	% Predicted	Predicted	Actual	% Predicted	Predicted	% Change
FVC (L)	3.78	74	5.02	4.53	90	5.02	19.84
FEV-1 (L)	2.83	70	4.07	3.52	86	4.07	24.38
FEF25–75 (L/S)	2.32	57	4.1	3.15	77	4.1	35.78

Abbreviations: FVC = forced vital capacity; FEV-1 = forced expiratory volume at 1 second; FEF25–75 = maximum mid-expiratory flow rate.

brane permeability is intact. On the other hand, an exudative pleural effusion is more of a local problem, resulting in increased permeability of the capillaries in the pleura (e.g., pneumonia), impaired lymphatic drainage from the pleural space (e.g., malignant effusion), or decreased pressure in the pleural space (e.g., complete lung collapse). This results in the formation of high-protein content of the pleural fluid, called exudates [5,6]. Determining whether the pleural fluid is a transudate or exudate requires measuring the protein and lactate dehydrogenase (LDH) in the serum and pleural fluid. Pleural fluid is exudative if it meets one of three criteria: 1) Pleural fluid protein to serum protein ratio of more than 0.5; 2) Pleural fluid LDH to serum LDH ratio of more than 0.6; 3) Pleural fluid LDH more than two thirds of the normal value of the serum. Pleural fluid is transudative if none of the above criteria apply [7,8]. In the case presented here, applying the above criteria yields exudative pleural fluid. In addition, the fact that eosinophils were 10% of the WBC of the pleural fluid indicates that the pleural fluid was eosinophilic too.

The great majority of exudative pleural effusions are caused by pneumonia, malignancy, and pulmonary embolism. If these major causes are ruled out, then causes of eosinophilic pleural effusion should be considered depending on the clinical picture. Those causes include traumatic hemothorax, tuberculosis, benign asbestosis, drug reaction, parasitic infections, and Churg-Strauss syndrome [7,9]. The patient presented here had no evidence of pneumonia whatsoever; he had no fever, no chills, no cough, and no sputum production. His serum WBC with the differential was within normal limits, and his CXR revealed no infiltrates. Malignancy was ruled out by the negative cytopathology of the pleural fluid for malignant cells. He also had negative CT of the chest. Pulmonary embolism was ruled out by a negative V/Q scan of the lung. Collagen vascular disease was considered unlikely, since antinuclear antibodies (ANA), rheumatoid factor, and antineutrophil cytoplasmic antibodies (ANCA) screens were negative, there were no other clinical findings that would suggest this etiology, and there were no other systemic effects.

Although eosinophils in the pleural fluid are not particularly helpful in narrowing the differential diagnosis, they are more likely to be associated with benign conditions and favorable prognoses [10,11]. Nevertheless, malignancy, tuberculosis, or pulmonary embolism can cause eosinophilic pleural effusion. If these conditions are ruled out and no obvious diagnosis is found, the subsequent work-up need not be aggressive [7,10].

Drug-induced pleural effusion is a well-described entity in the literature. In a patient like the one presented here, where the major causes of eosinophilic pleural effusion were excluded and the clinical picture didn't suggest the other minor causes, a drug reaction is worth considering. Drugs that are reported to cause eosinophilic pleural effusion are numerous [12,13]. However, there are few drugs that are well established to be associated with eosinophilic pleural effusion, and these are: Nitrofurantoin, dantrolene, valproic acid, propylthiouracil, isotretinoin, and bromocriptine [14].

In the patient we are reporting on, a drug reaction was suspected after excluding the other major causes of exudative pleural effusion. In addition, it was noted that there was a temporal relationship (6 weeks) between the initiation of treatment with tizanidine and the development of the pleural effusion. Therefore, the decision was made to discontinue tizanidine and observe the patient. Within a period of 1 month, the patient's symptoms improved markedly. His lung exam showed resolution of the dullness to percussion and clearing of the breath sounds on the right lung base. The pulmonary function tests improved significantly, as shown in Table 3, and his CXR revealed resolution of the pleural effusion.

It is unlikely that the pleural effusion was caused by baclofen, for baclofen was used for a maximum of 1 week, and the pleural fluid was

detected about 7 weeks after baclofen use. Moreover, the pleural effusion continued to worsen even 4 or 5 months later and persisted for about 8–9 months in total.

The limitations of this study include the following. First, there was an inadequate malignancy work-up. Some of the items that were missed in this work-up are CT scans of the abdomen and pelvis to rule out tumors and other gastrointestinal and pancreatic disorders that might cause pleural effusion. Moreover, flow cytometry on the pleural fluid was not done. Second, viral cultures on the pleural fluid were not done, and viral infections might cause exudative pleural effusion. Third, hematology/oncology consultation was not done. This would have helped with the malignancy work-up.

This is a novel report of an exudative pleural effusion in a patient presumably caused by tizanidine. Pleural effusion induced by tizanidine has not been reported previously in the literature. Whether this is a common side effect of tizanidine or a rare one is yet to be determined. Therefore, this report serves to draw the attention of physicians who use tizanidine and those who treat pleural effusions in patients who are on tizanidine to include the drug in their differential diagnosis, especially if all the work-up of an exudative, eosinophil-predominant pleural effusion comes back negative and no clear cause is found.

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