PRAMIPEXOLE INDUCED RECURRENT PLEURAL EFFUSION

CASE REPORT
PROF-1901

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ABSTRACT… Context: Recurrent pleural effusions are relatively uncommon and as clinicians we keep drug induced pleural effusion lower in our list of differentials. Pramipexole induced recurrent pleural effusion can be life threatening if not recognized early and has been reported in literature only a few times. **Case Report:** A 44 years old man with history of traumatic brain injury presented with pneumonitis and p leural effusion which was tapped. Patient returned with pleural effusion within 2 weeks and a careful analysis of all the risk factor and drugs revealed that the most likely etiology was chronic use of Pramipexole leading to recurrent pleural effusion and early pulmonary fibrosis. **Conclusions:** Pramipexole induced recurrent pleural effusion can cause significant morbidity and should be recognized early. Physician prescribing this medication should be aware of this rare side effect of the medication.

Key words: Pleural effusion, Pramipexole

INTRODUCTION

Approximately 1 million cases of pleural effusion are diagnosed in the USA each year and most common causes are congestive heart failure, malignancy, infections and pleural effusion. Rare causes can be easily missed or overlooked in the presence of co-morbid conditions.

CASE REPORT

A 44 year old Caucasian male with a history of hypertension, hepatitis C, accidental traumatic brain injury in 1990 and 2005, was being followed by the department of physical medicine and rehabilitation, for the worsening dystonia and immobility. He had a left lower extremity tendon release surgery in the past. He had a prolong disability and smoked about half a pack per day for the last 20 years. There was no history of drinking and illicit drug abuse. Patient had been on a baclofen pump to help his symptoms of increased muscle tone. Later on he was also treated with Depakote for the dystonic movement control. Patient improved with good trunk control and was able to move up to the wheel chair. About 6 months ago patient was put on a trial of Mirapex (pramipexole) and he responded very well with his symptoms. He was discharged from the nursing home and started standing up with the help of bars and assistance. His physiatrist increased the dose of Pramipexole with the obvious improvement in his motor symptoms.

About two months later patient presented to the hospital with pneumonia like symptoms. He was treated with a course of antibiotics and was discharged home. Of note, patient was also given a short 5 day course of oral steroids at this time. Within 30 days patient presented in the ER with dyspnea which was progressive and associated with a cough. Thoracentesis was performed, 480 ml of pleural fluid was tapped and pleural fluid analysis showed exudative picture with high eiosinophils. Patient‘s symptoms improved with thoracentesis but he redeveloped pleural effusion within 5 days.

Extensive workup for the possible etiology of pleural fluid was performed including pleural fluid analysis, CT of the chest. Please review the table below for the results.

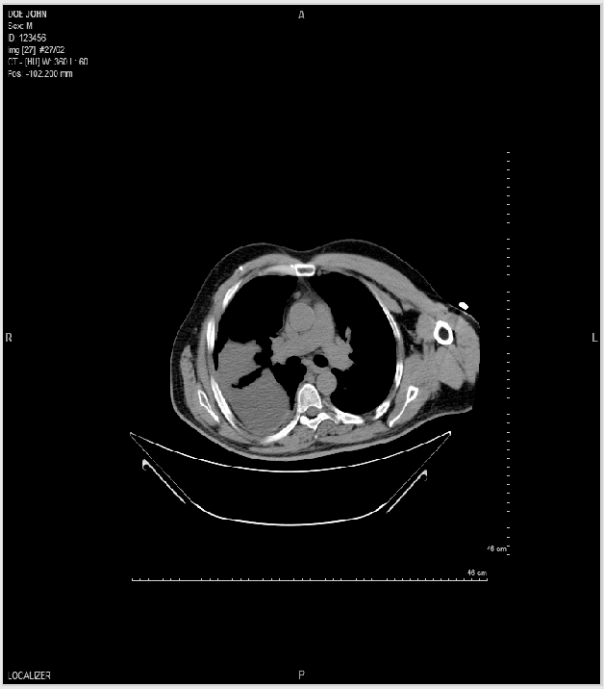
Cytology was negative for malignant cells. Workup for autoimmune disease and toxicology was negative. We could not find any parasitic etiology. Pulmonolgy and cardiothoracic surgery teams were consulted for the recurrent nature of pleural effusion. Later on patient required a chest tube in the right thorax.

After draining the effusion with thoracentesis for the first 2 times pleural effusion recurred within short period. After a careful review of literature for all the possible etiologies we stopped pramipexole and pleural effusion did not recur. The radiological features of ground glass appearance were moderately decreased. Family physician and pulmonologist will continue to follow the

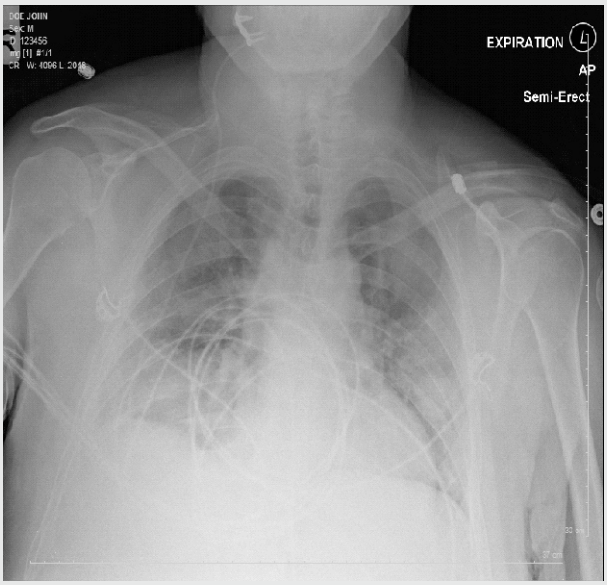
Table-I. Analysis of pleural fluid

Color	Red	Yellow
Appearance	Bloody	Cloudy
pH	7.39	7.32
Fluid RBCs	10000	2600
Fluid nucleated cells	449	170
Fluid neutrophils	7	4
Fluid eiosiphils	60	48
Fluid lymphocytes	15	26
Fluid Basophils	1	4
Glucose	84	109
Total protein	4.7	NA
Albumin	2.4	2.7
Amylase	36	31

CTscan finding of Pleural effusion



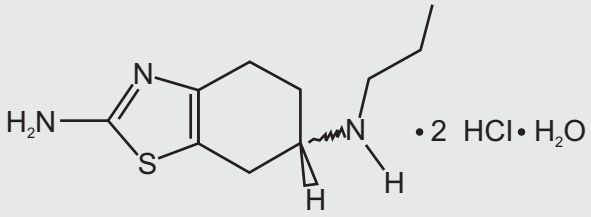
Pramipexole related Chest Xray findings



DISCUSSION

Dopamine agonists can be classified as ergot derived (pergolide and carbegoline) and non-ergot derivatives (Pramipexole and ropinirole). Pramipexole ((S)-N[6]-propyl-4,5,6,7-tetrahydro-1,3-benzothiazole-2,6-diamine) is a non-ergoline dopamine agonist used for the treatment of Parkinson's Disease and restless leg syndrome. It acts as an agonist at D2, D3 and D4 receptors. Off label uses include treatment of depression[1,2].

Pramipexole chemical structure



Fibrotic complications such as pulmonary fibrosis, retroperitoneal fibrosis, pleural thickening and peri-carditis have been reported in some patients treated with "ergot-derived dopaminergic agents" such as pergolide, and bromocriptine. It has been noticed that these complications may resolve when the drug is

discontinued; complete resolution is not always seen. A small number of reports have been received of possible fibrotic complications, including peritoneal fibrosis, pleural fibrosis, and pulmonary fibrosis in the post-marketing experience for Mirapex. Rare side effects like compulsive gambling and compulsive sexual tendencies have been reported in literature. Another side effect known as dropped head syndrome is around 6% in certain areas like Japan[6].

Pramipexole is mostly excreted through kidneys and the safe dose has not yet been fully investigated. A synergic effect between pramipexole and other drugs might amplify the severity of intoxication even though pramipexole is not overdosed especially in uremic patients[8].

A small number of reports have been received of possible fibrotic complications, including peritoneal fibrosis, pleural fibrosis, and pulmonary fibrosis, in the post-marketing experience for Pramipexole dihydrochloride. While the evidence is not sufficient to establish a causal relationship between Pramipexole dihydrochloride tablets and these fibrotic complications, a contribution of Pramipexole dihydrochloride tablets cannot be completely ruled out in rare cases. There have been 7 reported cases of pleural effusion as a side effect of Pramipexole therapy so far and most of these have been seen within 6 months of start of therapy[13].

Several mechanisms have been postulated for the pulmonary fibrotic reaction of ergot alkaloids including an idiosyncratic immune reaction and modulation at peripheral neurotransmitter or humoral receptor sites. As a result of fibroblast stimulation by various factors such as connective tissue growth factor which induces collagen type I and fibronectin, and the deposition of such molecules leads to fibrotic disease in many tissues. Serotonin receptor modulation has also been hypothesized.

Another related hypothesis is interference with pineal function, which is profoundly affected by serotonergic function[9]. Pinealectomy leads to increased formation of fibrous tissue in the abdominal cavity by reduced formation and/or action of prostaglandin E1 and thromboxane A2. Prostaglandin E1 plays an important role in enhancing function of T-suppressor lymphocytes that control overactive antibody-producing B lymphocytes in situations like collagen vascular diseases.

The possible explanation of eiosinophilia is a stimulation of pleural mesothelial cells by a non specific injury leading to production of chemokines, cytokines and adhesion molecule which cause eiosinophilic recruitment. Several mediators like eotaxins (eotaxin-1 [CCL11], eotaxin-2 [CCL24], and eotaxin-3 [CCL26]), interleukin (IL)-3, IL-5, granulocyte/macrophage stimulating factor (GM-CSF), and RANTES (Regulated upon Activation, Normal T-cell Expressed and Secreted) are involved in the recruitment of eiosinophils to the tissues. . Vascular cell adhesion molecule (VCAM-1) and eosinophil very late activation antigen (VLA-4) help with eiosinophilic and endothelial interaction. Soluble VCAM is markedly increased in eiosinophilic effusions as compared to non eiosinophilic effusions which possibly explain their pathogenesis.

CONCLUSIONS

More elaborate studies are required to understand the mechanism of pramipexole induced pleural effusion. Physicians prescribing pramipexole for Parkinson's disease and RLS should keep in mind these rare side effects of the drug in order to avoid adverse outcomes.

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Article received on: 24/12/2011 Accepted for Publication: 11/01/2012 Received after proof reading: 10/05/2012

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Article Citation:
Ghazi MA, Malik KS. Pramipexole induced recurrent pleural effusion. Professional Med J Jun 2012;19(3): 418-421.

The true traveler is he who goes on foot, and even then, he sits down a lot of the time.

Colette (1873 - 1954)