Case Report

ERGOTAMINE-INDUCED PLEURAL AND PERICARDIAL EFFUSION SUCCESSFULLY TREATED WITH COLCHICINE

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ABSTRACT

A 83-year-old woman was admitted to hospital with chest pain, fever, dry cough and palpitations. Chest X-ray revealed a pleural effusion, assumed to be caused by cardiac failure and respiratory infection. Despite treatment with antibiotics and diuretics, the pleural effusion increased on chest X-ray and there were signs of pleural and pericardial effusion on computed tomography (CT) scan. Treatment with non-steroidal anti-inflammatory drugs (NSAIDs) was not successful. Meanwhile patients' long-term use of ergotamine for migraine was revealed, which is associated with pleuropulmonary and cardiac fibrotic reactions. Tentative treatment with colchicine was successful, with complete resolution of pleural fluid, fever, cough and inflammatory parameters. This case highlights the importance of establishing an ergot alkaloid use registry in unexplained pleuropericardial effusions and supports the use of colchicine as a potential therapeutic approach.

Key words: ergotamine, pleural effusion, pericarditis, drug-induced pleural disease

CASE REPORT

A 83-year-old woman, previously in excellent medical condition, presented at the emergency department with complaints of severe retrosternal and interscapular pain, dry cough and palpitations since two days. She had a medical history of curatively treated ovary and breast carcinoma respectively 24 and 6 years ago and has suffered minor depressive symptoms for which she was taking citalopram.

Clinical examination revealed an irregular tachycardia of 130 beats per minute, bibasal lung crepitations and body temperature of 38.2°C. Blood analysis showed an elevated CRP (C-reactive protein) of 171 mg/L (normal reference < 5.0 mg/L). The heart was enlarged at chest X-ray, with limited bilateral pleural effusions, and a possible retrocardial pneumonia. The patient was treated for pneumonia with amoxicillin-clavulanate. A CT scan of the thorax confirmed bilateral pleural effusions, which were assumed to result from pneumonia and/or cardiac failure due to a new onset rapid atrial fibrillation. Initial cardiac ultrasound showed a normal cardiac function, but there was some thickening of the mitral valve. The patient was treated with loop diuretics and beta-blockers followed by clinical improvement. Because pleural fluid on chest X-ray decreased with a parallel decrease in blood CRP to 27 mg/L, she was discharged from the hospital.

Two weeks later, the patient was re-admitted due to increasing dyspnea with fever up to 38.9°C and an elevated CRP level (213 mg/L). Chest X-ray revealed substantial bilateral pleural effusions, which were initially treated as a recurrent respiratory infection, with secondary cardiac failure. Despite treatment with ceftriaxone and loop diuretics, fever continued and pleural effusions increased without any decrease in CRP levels. A new thoracic CT-scan revealed signs of pleuropericarditis: pleural and pericardial effusion, with contrast uptake in the pericardium. Pleural fluid analysis showed a protein content of 41 g/L and lactate dehydrogenase (LDH) of 280 U/L, compared to serum levels of 62 g/L and 319 U/L respectively, defining the fluid as exudate. As the patient had a history of malignancy, recurrence was excluded by fluorodeoxyglucose positron emission tomography (FDG-PET) and absence of malignant cells on cytology examination of the pleural effusion. FDG-PET was also not compatible with possible other inflammatory diseases including giant cell arteritis. Serum titers for antinuclear antibodies were absent. Screening for infectious agents including bacterial blood –and sputum cultures and Mantoux test

were negative. Serology for adenovirus, hepatitis virus, cytomegalovirus, human immunodeficiency virus and parvovirus proved also to be negative; repeated Coxsackie virus serology could not reveal a recent infection either. There was no history of exposure to asbestos. Although the causative agent was unknown, treatment with NSAIDs was initiated with ibuprofen 600 mg three times daily. Hereunder, CRP levels decreased from 90 mg/L to 42 mg/L after five days. Chest X-ray also showed some reduction in pleural effusions and the patient was discharged from the hospital. Five days later she represented at the emergency department with recurrent dyspnea and fever. CRP was elevated to 96 mg/L. Chest X-ray (Figure 1) showed an increase in pleural fluid. Pleuroscopy was performed to exclude pleural malignancy: bioptic and cytologic examination showed granulation tissue and numerous macrophages as signs of clearance response. A temporary thoracic drain was inserted.

Because the causative agent remained unclear, a renewed history was taken. The patient now mentioned her regular and prolonged use of ergotamine and caffeine (Cafergot®) because of a recurrent migraine that had not reappeared since her initial admission. She did not consider this as being relevant since she only took a very small dose (about a quarter, i.e.. 0.25-0.50 mg ergotamine) via suppository daily, however she took this for almost 50 years. Initially, her usage of ergotamine was discontinuous with regular drug-free episodes of maximally two weeks. The last 5 years, ergotamine was taken on daily basis.

The standard treatment for ergot-induced pleuropericarditis is to discontinue the intake of the provoking drug but in this case, symptoms did not resolve after several weeks and the patient relapsed twice. Therefore, we initiated a therapy with colchicine at 1 mg daily. Under this therapy, CRP decreased from 38 mg/L to a normal value (< 5 mg/L) in 7 days and we saw a rapid clinical and radiological remission. Magnetic resonance imaging (MRI) of the heart at that time showed a pericardial effusion without signs suggestive of constriction. The patient was discharged a week after starting the treatment with colchicine, in good overall condition.

Ambulatory follow-up 4 weeks after starting colchicine therapy was favourable, with normal clinical, biochemical and radiological findings on chest X-ray (see Figure 1). At that time the dose of colchicine was reduced to 0.5 mg daily. The patient remained symptom-free so that after another month, treatment with colchicine was stopped. Ambulatory evaluation 2 months later showed no clinical or radiological signs of relapse.

DISCUSSION

Cafergot® is a combination drug, approved by the FDA in 1960 to treat migraine headache. It contains both caffeine and ergotamine, the latter belonging to the family of the ergot alkaloids. Ergotamine causes vasoconstriction of vascular smooth muscle by partial agonist effects at α adreno-and vascular 5-HT (serotonin) receptors. The anti-migraine action of ergot alkaloids is thought to be egulated by serotonin receptors. Ergotamine modulates intra and extracranial blood flow leading to a decrease in the amplitude of pulsations of the cranial arteries, and to reduced hyperperfusion of the basilar artery territory (7). The drug is available in Belgium in tablets or rectal suppositories, combined with caffeine to enhance absorption.

We describe the case of a 83-year old woman who developed sudden pleuropericardial effusions associated with chronic use of low-dose ergotamine for migraine headache. The chronic use of ergot alkaloids is known to be associated

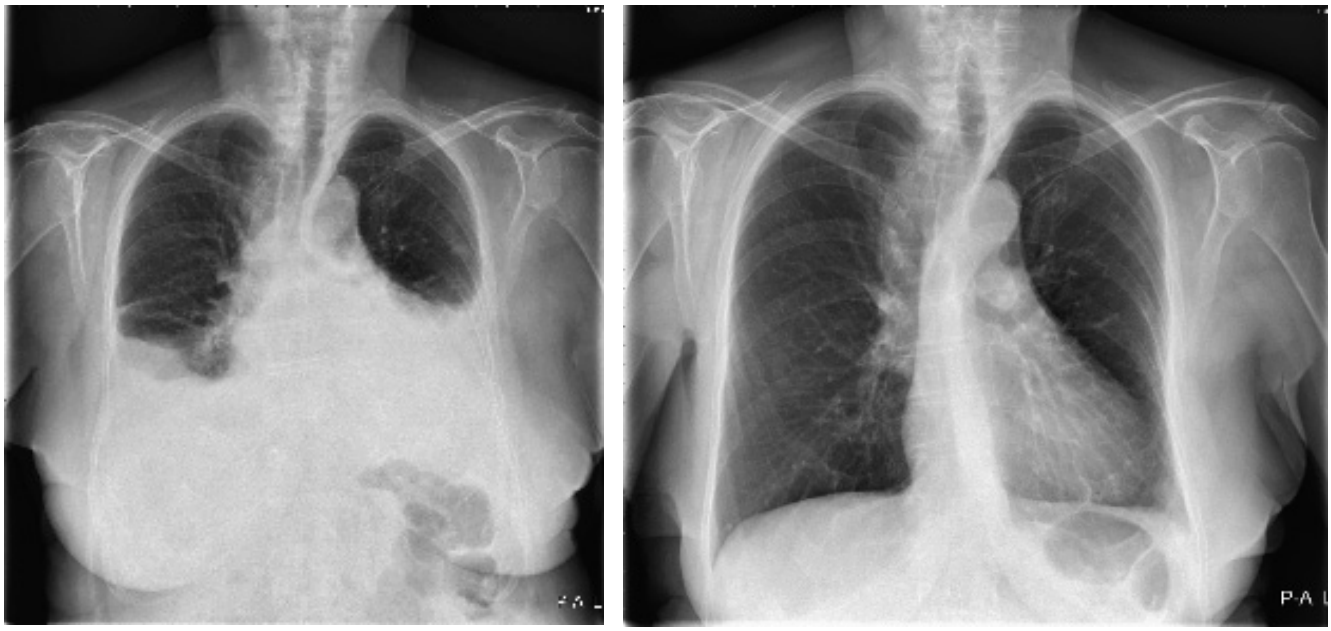

Figure 1: *Patients' chest X-ray.*
Left: at third admission in hospital. *Right: 4 weeks after treatment with colchicine.*

with connective tissue proliferation in the retroperitoneal space, the pleural cavity and pericardial/endocardial tissues, which can lead to cardiac murmur or valvular damage (1, 2, 5). For this reason methysergide, an amine ergot alkaloid, was withdrawn in the USA, while it is still available in Belgium.

The event scored 7 points on the Naranjo scale3, a scale developed to assess the likelihood and causality of adverse drug events. A Naranjo score between 5 and 8 rates the event as "probably" due to chronic treatment with ergotamine.

The exact mechanism which causes the fibrotic reactions is a matter of debate, but serotonin-induced fibrosis is one possible explanation through its action on 5-HT2b receptors. A recent study confirmed the increased expression of 5-HT2a/b receptors in idiopathic lung fibrosis with decreased fibrotic reaction and improved lung function after the administration of terguride, a 5-HT2a/b antagonist, hereby supporting the evidence for a dominant role of serotonin in this disease (4).

Because symptoms initially progressed after drug discontinuation, additional treatment with NSAIDs was initiated. However, the disease relapsed under treatment with ibuprofen and therefore therapy with colchicine was initiated based on recent studies promoting colchicine as the agent of choice for treatment of pericarditis, even in first line (5). Its combined anti-inflammatory properties seem very attractive in the treatment of our patient's condition, believed to be acting through β-tubulin binding, a component of the cell cytoskeleton, indispensable for a variety of cellular motility functions including chemotaxis, phagocytosis and degranulation. Binding to β-tubulin blocks the dynamic formation of microtubules causing decreased mobility of leucocytes and phagocytes, thereby decreasing inflammatory reactions. Besides β-tubulin binding, several other cardinal mechanisms of action have been described, including the inhibition of IL-1 production (6).

Because colchicine accumulates in leucocytes, an adequate response can be reached at low oral doses. The maintenance dose for acute pericarditis is usually 1 mg a day, divided into 2 gifts for three months. Pain relief is achieved within 12-24 hours if adequately dosed. Under this therapy, our patient showed rapid clinical, biochemical and radiological improvement.

CONCLUSION

Causes of pleuritis/pericarditis can be uncommon and require several investigations. This case highlights the importance of preceding ergot alkaloid use registry in unexplained pleuropericardial effusions. Chronic use of this drug class should be discouraged. To our knowledge, this is the first report of ergotamine-induced pleuropericarditis successfully treated with low dose colchicine.

CONFLICT OF INTERESTS: None.

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