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CASE REPORT

A patient with tremors and breathlessness

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Side effects of Pergolide treatment;
Parkinson's disease

Summary We describe a patient with Parkinson's disease who developed bilateral pleural effusions and pleural fibrosis associated with pergolide therapy. Pergolide is an ergot-derived dopamine agonist used in the treatment of Parkinson's disease. This case report illustrates that physicians should have a high index of suspicion and consider drug-induced adverse effects in any differential diagnosis.

Case report

A 54-year-old male diagnosed with Parkinson's disease five years previously, presented with increasing breathlessness and cough of three months duration. He was a self-employed painter and his general practitioner had suspected a diagnosis of asthma although there had been minimal response from inhaled therapy. He was a non-smoker with no history of exposure to tuberculosis or asbestos. There was no past medical history suggestive of cardiac, pulmonary or connective tissue disorders. His medication included Co-careldopa 10 mg/100 mg three times daily, Co-beneldopa three tablets in the morning, Co-careldopa 50 mg/200 mg 1 tablet at night, and pergolide which had been gradually increased to 1.5 mg three times daily since its introduction three years previously.

On admission there were no peripheral signs of congestive cardiac failure and auscultation revealed reduced breath sounds and crackles at both lung bases. Chest x-ray showed bilateral pleural effusions (Fig. 1). Abnormal blood investigations included a monocytosis of 1.68×10^9/l (0.2—0.8), an elevated erythrocyte sedimentation rate of 90 mm/h (5—15) and C - reactive protein level of 143 (<5). Antinuclear antibodies were weakly positive at a dilution of 1:30. Serum electrophoresis and urine for Bence Jones protein were normal. Electrocardiogram, perfusion lung scan and echocardiogram were also normal. X-rays of thoraco/lumbar spine and bone scan suggested a suspicious sclerotic lesion in the T8 vertebra. This was later confirmed as early Paget's disease of the spine. CT scan of the chest and abdomen demonstrated bilateral pleural effusions with pleural thickening at both the lung bases (Fig. 2). In addition, there were enlarged right para-tracheal and hilar lymph nodes at 1.3 and 1.6 centimetres respectively. Thoracocentesis of the left pleural effusion revealed a blood-stained transudate (Pleural fluid protein 23 gm/l;

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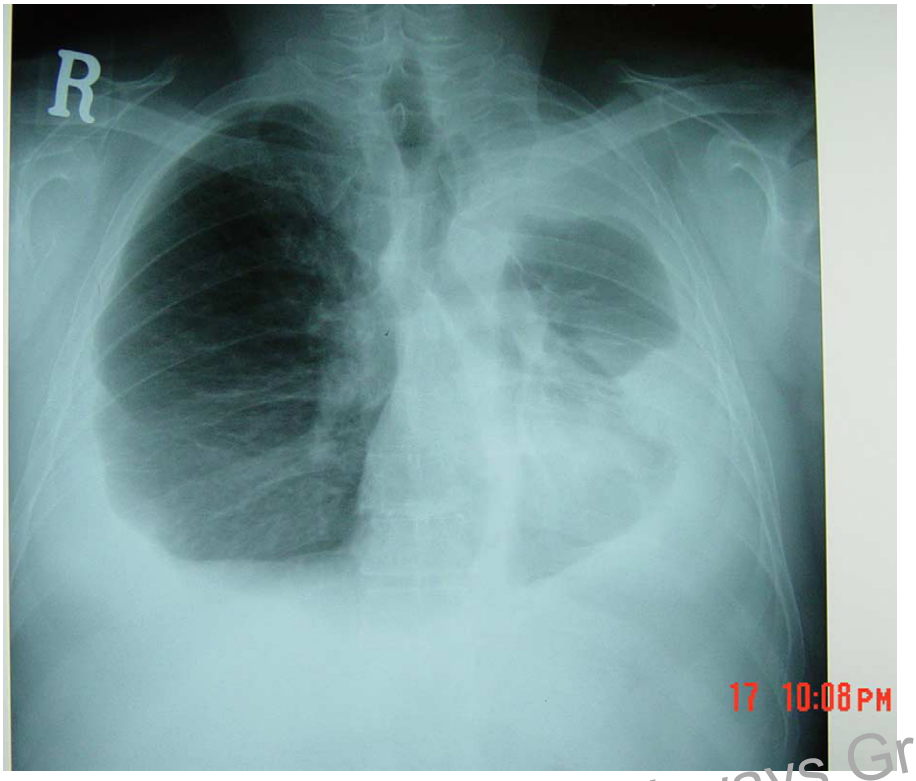

Figure 1 PA chest radiograph shows bilateral pleural effusions.

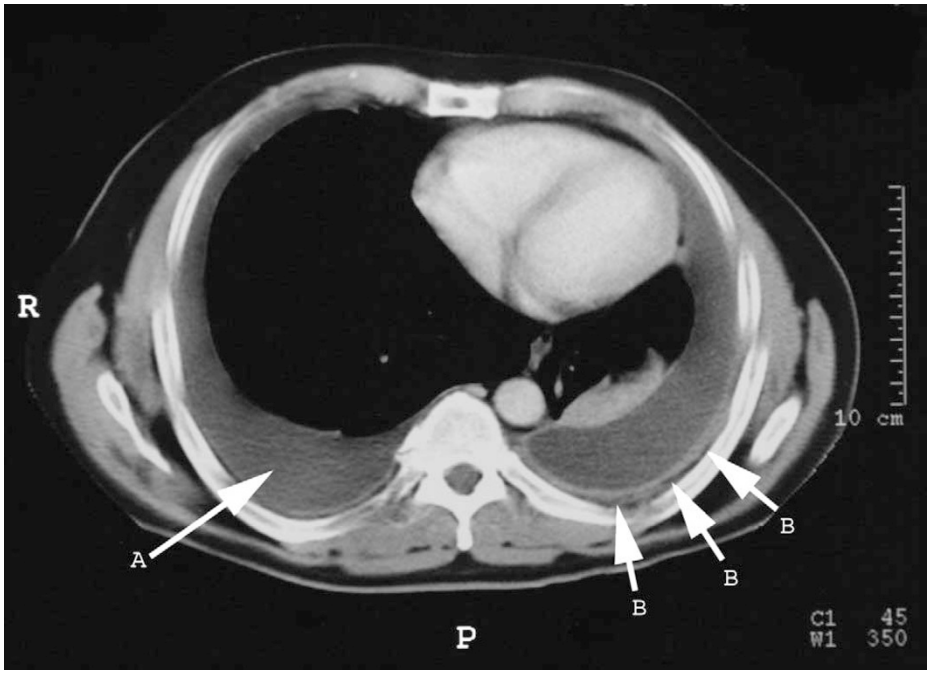

Figure 2 Axial CT of the thorax confirms bilateral pleural effusions (single arrow). Smooth pleural thickening is more marked on the left side (multiple arrows).

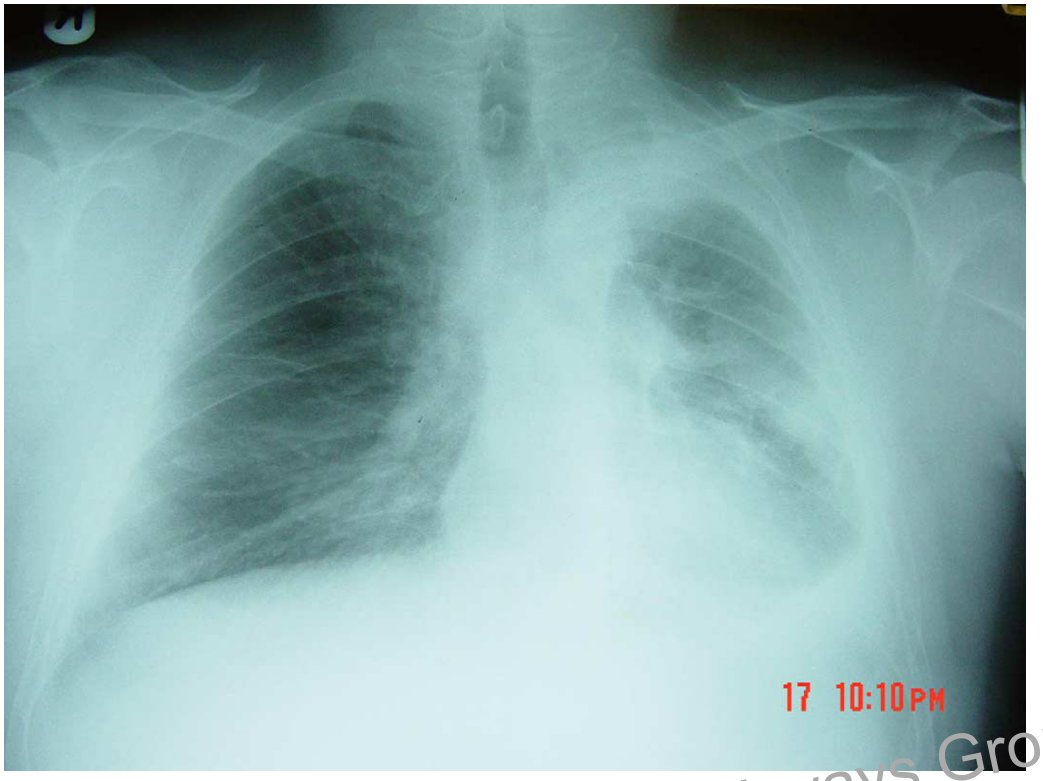

Figure 3 PA chest radiograph shows persistent left-sided pleural effusion/pleural thickening with resolution of right-sided changes.

Serum protein 74 gm/l, with few lymphoid cells and no malignant cells on cytology. Gram stain and culture sensitivity of pleural fluid for bacterial organisms was negative. The patient was treated with antibiotics and thoracocentesis with resulting improvement in breathlessness.

One month later he was readmitted with increasing breathlessness and weight loss. Chest x-ray showed reaccumulation of the bilateral pleural effusions and a possible 3-centimetre mass lesion along the left costal margin. Bronchoscopy was normal as were serum calcium and tumour markers. Repeat CT scan of the chest again showed bilateral pleural effusions and pleural thickening. There was resolution of the mediastinal lymphadenopathy and no intrapulmonary lesions were identified.

Multiple negative investigations and the absence of well-recognised causes of recurrent pleural effusions raised the possibility of drug-induced disease. Ropinirole 2 mg three times daily was substituted for pergolide and a reducing course of prednisolone was started at a dose of 30 mg once daily. Six weeks later there had been an improvement in his breathlessness and he had regained his lost weight. Chest x-ray at that time showed a reduction in the size of the pleural effusions. At eighteen months follow-up, there was significant improvement in his exercise tolerance but with residual left pleural changes on chest X-ray (Fig. 3).

Discussion

There is now growing evidence for the use of dopamine agonist monotherapy in the treatment of Parkinson's disease especially in younger patients [1]. Pergolide is one such ergot-derived dopamine agonist used in the treatment of Parkinson's disease. Following the first description in 1966 [2], many case reports since have described the association of serosal fibrosis with the use of ergoline drugs such as methysergide, ergotamine, pergolide, bromocriptine and cabergoline [3]. In one database analysis of adverse drug reports on anti parkinsonian drugs, serosal fibrosis constituted 87 out of a total of 1902 (4.6%) adverse drug reactions reported with pergolide, compared to 2.3% and 0.1% with Bromocriptine and Levodopa/Carbidopa combination respectively [6].

Retroperitoneal fibrosis, constrictive pericarditis, pulmonary fibrosis, pleural fibrosis and pleural effusion, are included in the spectrum of adverse drug reactions reported with pergolide [4—7].

Recently tricuspid regurgitation requiring valve replacement has been associated with the use of pergolide therapy [8]. The pathological appearances of the valves were reported to be similar to carcinoid disease and with the use of anorectic agents fenfluramine and dexfenfluramine, further strengthening the seratonergic effect of pergolide as the causative mechanism.

Literature on pergolide-induced pleuro-pulmonary changes reveal a mean dosage of 3 milligrams and a latent period of 2 years between the emergence of symptoms and the introduction of pergolide [4—7]. Erythrocyte sedimentation rate when measured was raised in all but one cases. Pleural effusions can be transudate or exudate and may show eosinophilia. Pleural biopsies reveal fibrous tissue with sparse inflammation. Withdrawal of the offending drug usually results in improvement of symptoms with residual changes in some. The role of steroids in enhancing the resolution of these changes remains unproven. Rare incidences of non-resolution as in our case and fatality have been reported with the use of pergolide therapy [6].

This case illustrates that patients are often subjected to extensive diagnostic investigations before such drug-induced changes are suspected. Indeed, drug-induced side effects should always be considered in any differential diagnosis. With the growth of the elderly population and the likely increase in the prevalence of Parkinson's disease [1], physicians should be increasingly aware of the side effects caused by ergoline drugs, which may be irreversible. We would support monitoring of pergolide therapy with an annual chest x-ray and measurement of the erythrocyte sedimentation rate as suggested by Shaunik et al. [4], especially during prolonged treatment or if the dosage of pergolide has been recently increased.

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