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Brief report

Suggestive evidence for bromocriptine-induced pleurisy

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Abstract

Pleurisy of initially unknown origin was found in a patient who was treated with bromocriptine for Parkinson's disease for 6 years. At presentation, bilateral pleural thickening existed that caused severe restriction of pulmonary function. There were an elevated erythrocyte sedimentation rate, polyclonal hypergammaglobulinaemia, increased levels of acute phase proteins and anaemia. After withdrawal of the bromocriptine the patient's complaints as well as the laboratory parameters markedly improved. Further loss of pulmonary function did not occur. However, the pleural thickening did not resolve, not even upon subsequent corticosteroid treatment, probably due to fibrosis. Together, these findings strongly suggest a causative role of bromocriptine. The results of the laboratory studies suggested an immunopathogenetic mechanism, but in vitro lymphocyte-proliferation studies and skin patch tests with bromocriptine were negative. Bromocriptine should be considered as a cause of pleurisy. The drug must be stopped immediately upon the occurrence of pleural thickening in order to prevent impairment of pulmonary function. In addition, periodic laboratory and X-ray studies in patients on long-term bromocriptine treatment should be considered.

Keywords: Pleurisy; Pleural fibrosis; Adverse reaction; Bromocriptine

1. Introduction

Pleurisy can be a manifestation of a large number of different clinical entities, such as infectious, malignant or autoimmune diseases or toxic conditions. Here we report on a case of bilateral pleurisy associated with the use of bromocriptine for Parkinson's disease.

2. Case report

A 66-year-old man suffering from mild Parkinson's disease for 15 years was admitted in September 1993 because of progressive thoracic discomfort, dry cough and dyspnoea that had existed for 7 months. An involuntary weight loss of 5 kg had occurred in this period. Neither the patient nor his family had a history of pulmonary, cardiac or other systemic diseases. He had been a heavy smoker but stopped smoking 20 years ago. He denied occupational exposure to asbestos. His medication consisted

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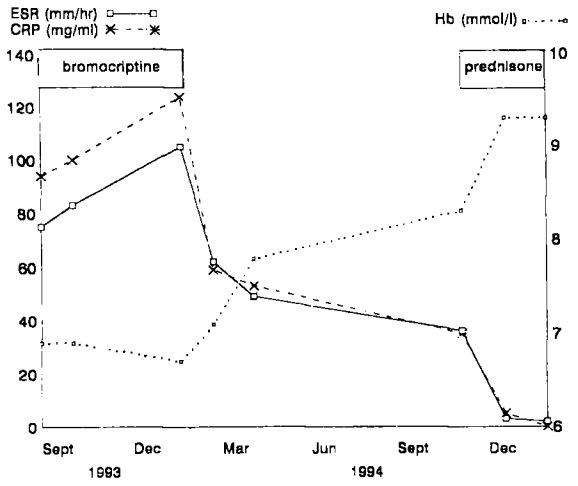

Fig. 1. Laboratory parameters (ESR, the concentration of C-reactive protein and haemoglobin) during bromocriptine treatment (15 mg daily), after withdrawal of this drug and during prednisone treatment (20 mg daily).

of bromocriptine (10–15 mg daily since 1987), levodopa-carbidopa and baclofen.

Physical examination disclosed no abnormalities other than bilaterally slightly dimmed percussion of the latero-basal thorax with fine inspiratory crackles, but was otherwise unremarkable. The temperature was 37.3°C. Laboratory studies showed a normochromic, normocytic anaemia, an elevated erythrocyte sedimentation rate and CRP concentration (Fig. 1) as well as increased levels of the acute-phase proteins haptoglobin (3.4 g/l, normal range 0.4–2.5 g/l) and ferritin (473 μg/l, normal range 30–240 μg/l). Analysis of the serum protein spectrum revealed increased levels of α_2-globulins and a polyclonal hypergammaglobulinaemia. IgG, IgA and IgM concentrations were 25.4 g/l (normal range 8.0–18.0 g/l), 4.84 g/l (normal range 0.9–4.5 g/l) and 1.26 g/l (normal range 0.6–2.8 g/l), respectively. The white-blood-cell count was just below the upper normal limit (9.8×10^9/l, 72% neutrophils, 20% lymphocytes, 8% monocytes). Autoantibodies (ANA, anti-ds-DNA, rheumatoid factors) were not detectable. Arterial blood gas analysis was normal.

The chest X-ray showed bilateral laterobasal pleural thickening with partial compression atelectasis of the left lung (Fig. 2c). A previous chest X-ray made in 1984 because of transient coughing was normal (Fig. 2a). The chest X-ray made in 1991, also because of transient coughing, showed only blunting of the costo-phrenic sinuses, a pleural streak in the midfield of the left lung and small pleural adhesions above the right diaphragm and beside the apex of the

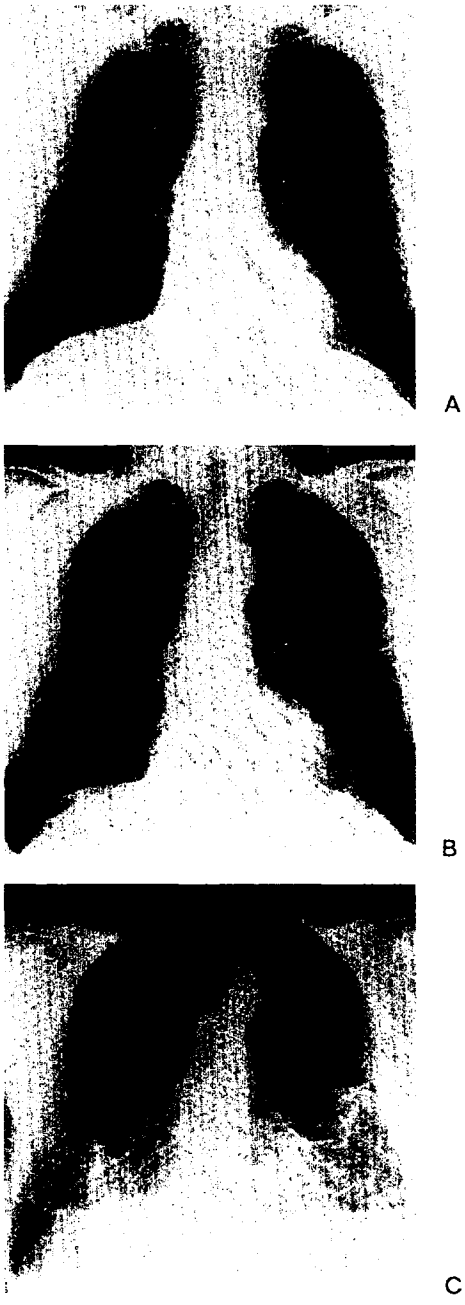

Fig. 2. Chest X-ray films 3 years before (A), during 4 (B) and 6 (C) years of treatment with bromocriptine for Parkinson's disease.

heart (Fig. 2b). Further investigations or follow-up chest X-ray studies were not carried out at that time. The findings on the present X-ray were confirmed by CT-scan. Neither parenchymal abnormalities of the lungs nor enlarged thoracic or abdominal lymphomas nor retroperitoneal fibrosis were present. Pleural fluid could not be obtained by puncture and was not demonstrated by subsequent echography. Pulmonary function tests showed a restrictive disorder (TLC 66%, FRC 61% of the predicted value) without airway obstruction.

Further aetiological studies including bronchoscopy with transbronchial biopsy, cultures of the sputum and PPD-skin test were all unremarkable. In the meantime the complaints of the patient worsened as did the results of the laboratory studies: the ESR and CRP concentration rose further, and the haemoglobin concentration further decreased (Fig. 1). Because of several reports that suggested a relation between pleuropulmonary disease and the use of bromocriptine [1–9] we conducted in vitro and in vivo immunological studies to confirm bromocriptine hypersensitivity as the aetiological factor in our patient. Skin patch tests and in vitro lymphocyte-proliferation studies using the patient's peripheral blood mononuclear cells were carried out with different concentrations of bromocriptine mesylate (final concentrations ranging from 0.2 to 125 ng/ml; therapeutic plasma concentration in Parkinson's disease patients ranging from 0.4 to 1.3 ng/ml). Both tests were negative with positive responses to control antigens.

Notwithstanding these results, we discontinued the bromocriptine medication by tapering it off in 2 weeks time. Four weeks after the bromocriptine had been completely stopped, the patient reported a substantial improvement of the thoracic discomfort, disappearance of the dry cough, reduction of dyspnoea and a weight gain of 3 kg. The laboratory abnormalities also improved (Fig. 1). The IgG concentration in the serum decreased slightly to 21.8 g/l. Although the complaints and laboratory abnormalities further declined in the next months, they remained at a lower level and the X-rays of the chest showed no improvement. Therefore, prednisone 20 mg daily was instituted. Within 6 weeks, the remaining thoracic discomfort and dyspnoea completely resolved. Laboratory parameters normalized (Fig. 1), including the hypergammaglobulinaemia (IgG and IgA concentrations declined to 14.8 and 2.84 g/l, respectively). However, neither the chest X-ray and the CT-scan nor the pulmonary function tests (TLC 68%, FRC 61% of the predicted value) showed any improvement. The corticosteroid therapy is currently being tapered off without any sign of reactivation of the inflammatory process.

3. Discussion

Long-term bromocriptine therapy has been used world-wide over the past two decades in large numbers of patients. Indications for bromocriptine include Parkinson's disease, prolactinoma and acromegaly. More recently, it has been used in inflammatory diseases such as arthritis psoriatica [10] and iridocyclitis [11], and in immunosuppressive regimens after transplantation [12,13], because bromocriptine interferes with the intracellular signalling of several cytokines [14]. However, to our knowledge, to date, only 30 cases of bromocriptine-induced pleurisy have been described in the English language medical literature [1–9,15]. This suggests that pleurisy is a rare complication of the use of bromocriptine. Alternatively, it is also possible that bromocriptine is often not recognized as a causative agent in patients with pleurisy. Upon introduction of bromocriptine, initial studies on the safety of this drug described pleurisy in 6 out of 123 patients treated [1]. The daily doses in that study were substantially higher than those used nowadays and ranged from 30 to 100 mg. This might explain the relatively high frequency of pleurisy in those patients. However, more recently pleurisy was also found in 2 out of 62 patients with Parkinson's disease taking less than 30 mg daily in a prospective 5-year follow-up study on the use of bromocriptine [15]. Similarly to our patient, all patients described until now were men over 50 years of age treated for Parkinson's disease. In all cases complaints and abnormalities in laboratory and X-ray investigations developed after 1–5 years of treatment with bromocriptine in daily doses of at least 15 mg. Retrospectively, it might be argued that the mild abnormalities present on the chest X-ray film of our patient in 1991 were also caused by bromocriptine.

In addition, pleural effusion with non-specific lymphocytic pleocytosis was frequently described [1–9,15]. Our patient, however, had no detectable amounts of fluid in the pleural cavity. Presumably, he had a more advanced stage of pleurisy with organisation and subsequent fibrosis of the pleural exudate that had been present earlier in the disease. The poor response to withdrawal of bromocriptine and the subsequent institution of prednisone therapy, as indicated by the X-ray studies and pulmonary function tests, support this hypothesis.

The striking relation between the withdrawal of bromocriptine in this patient and those described previously [1–9] and the improvement of the clinical and laboratory findings provides strong circumstantial evidence for a causative role of bromocriptine in the development of pleurisy. However, the pathogenesis is unclear. Idiosyncrasy cannot be ruled out, but the increased levels of acute-phase proteins and the polyclonal hypergammaglobulinaemia suggest that immunological mechanisms might be operating. To our knowledge we are the first to address this possibility by immunological studies. Definite proof is lacking as the skin tests and lymphocyte stimulation tests were negative. This might be due to the fact that bromocriptine does not provoke an immune reaction directly, but merely acts like a hapten, which together with pleural determinants forms the antigenic stimulus for immunologically mediated injury. In addition to pleural fibrosis, bromocriptine has also been implicated in the development of retroperitoneal fibrosis with similar abnormalities in laboratory studies, suggesting a common pathogenetic mechanism [4,15–18]. Fibrotic inflammatory disorders of the pleura and retroperitoneal fibrosis have also been descibed during the long-term use of the alkylated ergot derivative, methysergide, which has a molecular structure related to that of bromocriptine [19–21]. Direct proof that methysergide plays a causative role in these disorders is also lacking, but the abnormalities remitted after withdrawal of the drug, as we described for bromocriptine.

In conclusion, bromocriptine should be considered as a causative agent when pleurisy occurs, even if the daily dose is low. In such cases the drug should be stopped and corticosteroid treatment is possibly beneficial in order to prevent formation of irreversible pleural thickening with impairment of pulmonary function. In addition, periodic laboratory and X-ray studies in patients on long-term bromocriptine therapy are recommended.

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