

CASE STUDY

Low dose cabergoline induced interstitial pneumonitis

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Low dose cabergoline induced interstitial pneumonitis. W. Frank, R. Moritz, B. Becke, R. Pauli. ©ERS Journals Ltd 1999.

ABSTRACT: Certain dopaminergic anti-Parkinson drugs (ergolines) have repeatedly been identified as a cause of pleuropulmonary disease with a focus on serosal cell damage. Recently, a pathogenetic link between ergolines and prior asbestos exposure was suggested, as regards the development of pleural pathology. This report describes a patient with idiopathic Parkinson's disease, who was on a multiple drug regimen including low dose cabergoline. The patient developed a febrile illness with widespread bilateral lung infiltrations nonresponsive to β -lactam and macrolide antibiotics. Bronchoalveolar lavage and transbronchial lung biopsy showed a "hypersensitivity-like" interstitial lung disease, which cleared almost completely within 2 months after simple drug withdrawal. Circumstantial evidence suggests a so far undescribed adverse lung reaction to cabergoline, devoid of the more usual pleural changes.

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Long-acting synthetic dopaminergic drugs, collectively termed ergolines as utilized in the treatment of migraine and Parkinson's disease, are a rarely-recognized cause of pleuropulmonary disease. Some 70 case reports have been compiled since the first description [1], mainly in the form of pleural damage in terms of effusion and both visceral and parietal pleural thickening [2]. Recently, an interactive link between asbestos and ergoline-induced pleural changes by unknown synergistic mechanisms was suggested based on 15 case reports, where the association of the two causes was present [3]. Less frequently observed pulmonary involvement includes associated infiltration and/or fibrosis of areas adjacent to the pleural lesions [1, 2, 4, 5]. The occurrence of a lone pneumonitis linked to long-term cabergoline intake has, to the authors' knowledge, not been previously described. This study reports a case of an interstitial pneumonitis with histological data in a patient with Parkinson's disease which was readily and almost completely reversible after drug withdrawal, thus providing strong evidence for a causal relationship to the drug.

Case report

A 65 yr-old male with a 12-yr history of idiopathic Parkinson's disease was admitted to the authors' hospital for the diagnosis and treatment of bilateral pulmonary infiltrates, which had proven refractory to an 8-day standard regimen of oral cephalosporin (cefuroxim 500 mg) and a 14-day oral course of macrolide (roxithromycin 300 mg). He had developed occasional temperatures up to 39°C and a dry cough only a couple of days prior to induction of antimicrobial chemotherapy. Nonspecific symptoms such as significant weight loss (5 kg) night sweat, exertional

dyspnoea, weakness and malaise had been present 3 weeks earlier. There was no chest pain. The patient had continuously been on anti-Parkinson drugs for at least 10 yrs. These included pergolide (4.5 mg·day⁻¹), clozapin (25–50 mg·day⁻¹), carbidopa/levodopa (100/400 mg·day⁻¹) and benserazid (4 mg·day⁻¹). Four months prior to the development of nonspecific symptoms, clozapin had been substituted by the new anti-Parkinson drug cabergoline (1 mg·day⁻¹). The patient had reportedly suffered from allergic rhinitis and professional flour dust allergy for 10 yrs until 1985, but had remained nonsymptomatic after cessation of his baker activity. Likewise, no other environmental or occupational factors relevant to airborne alveolitis such as exposure to birds or moulds could be revealed. He had quit smoking 20 yrs before.

Physical examination was unremarkable except a subtle tremor, in particular there were no rales or crackles on auscultation. Standard radiography studies revealed multiple patchy and confluent ground glass peripheral consolidations preferentially in the middle and the left lower lobe (fig. 1). No unequivocal pleural changes were noted. Computed tomography confirmed several localized alveolar densities distributed across both lungs with some air bronchograms. In addition nodular lesions were noted in the left lower lobe (fig. 2).

Relevant laboratory results were a significantly accelerated erythrocyte sedimentation rate (ESR) (70 mm·h⁻¹), a moderate leukocytosis (10.4 cells·nL⁻¹) and a slightly elevated C-reactive protein (CRP) (25.08 mg·L⁻¹). Serological studies were negative for *Legionella* spp. (*Legionella*-antigen, immunofluorescence, complement fixation reaction (CFR), *Chlamydia* spp. (enzyme immune assay (EIA)-immunoglobulin (Ig)A, IgM, IgG), and epidemiologically

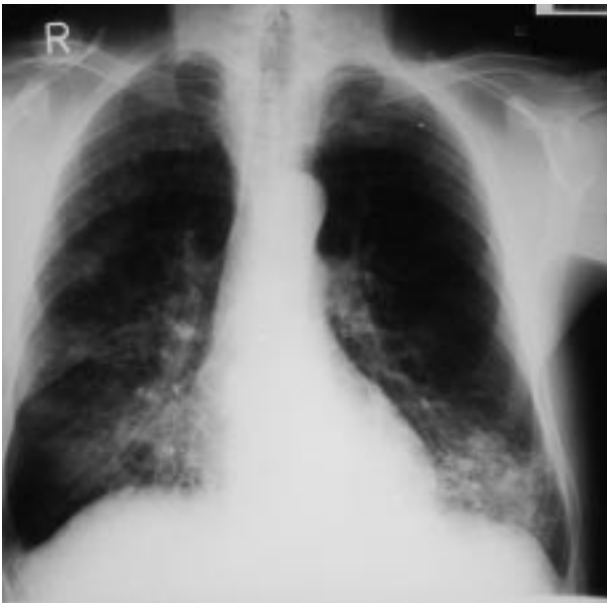


Fig. 1. – Chest radiograph prior to drug withdrawal (20 January 1998) showing bilateral infiltrates.

relevant Coxsackie (A9, A23, B1-6) and ECHO virus (3, 6, 7, 11, 25, 30) serotypes (neutralization test (NT) <1:10). Moderately positive titres were recorded for Parainfluenzae virus (IgG 1:430), Influenzae B virus (1:260) and *Mycoplasma pneumoniae* (1:350). However, no titre change was noted on a control 14 days later. Allergy testing resulted in marginally elevated specific IgE levels for rye and wheat with a normal total IgE ($84.95 \text{ IU}\cdot\text{mL}^{-1}$). Slightly elevated levels of precipitating IgG-antibody ($22.5 \text{ U}\cdot\text{mL}^{-1}$) were only detected for *Aspergillus fumigatus*. Other relevant serological findings included negative/normal values for antistreptolysin (ASL), rheumatoid factor (RF), angiotensin converting enzyme (ACE) and cyto-

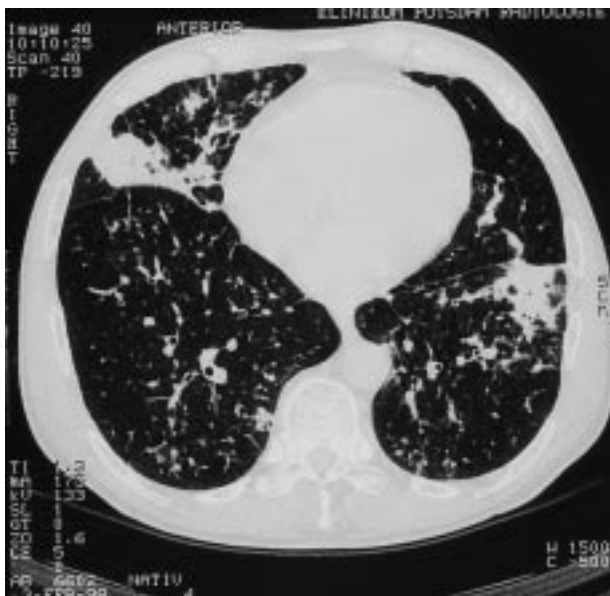


Fig. 2. – Computed tomography scan of the thorax (3 February 1998) revealing bilateral patchy densities.

plasmic/perinuclear (c/p)- antineutrophil cytoplasm antibody (ANCA). The human leukocyte antigen (HLA)-type screening revealed a B-27-positive status.

Regarding lung function, there was no impairment in both static and dynamic ventilatory function as well as gas exchange for carbon monoxide (vital capacity (VC) 109% of predicted, total lung capacity (TLC) 105% pred, forced expiratory volume in one second (FEV₁) 104% pred, transfer factor of the lung for carbon monoxide ($T_L\text{CO}$)/ alveolar volume (VA) 99% pred). Initial capillary blood gas analysis indicated a mild hypoxaemia (arterial tension (P_{a,O_2}) 9.5 kPa, alveolar to arterial oxygen difference (DA_{a,O_2}) 4.8 kPa) with no further fall on 90 W steady state exercise.

With proven nonresponsiveness to antibiotic treatment, more invasive investigations with the recovery of BAL fluid and transbronchial biopsies (TBB) were performed. Quantitative cultures of the BAL fluid did not grow pathogenic organisms. With a total cell count in the normal range ($3 \times 10^6 \text{ cells}\cdot\text{mL}^{-1}$) the differential count revealed 28.8% macrophages, 60% lymphocytes and 11.2% neutrophils. Results of lymphocyte subpopulation determination were: CD19+ 1%, CD3+ 88%, CD4+ 37%, CD8+ 50% (ratio 0.7), leukocyte (Leu) 7+ (CD57+) 9%, activated lymphocytes (CD3DR) 68%. Histological examination of representative tissue samples from the middle lobe (5th segment) showed a desquamative alveolitis pattern with mostly foam cell-like macrophages. A moderate thickening and round cell infiltration of alveolar septae with some contributing neutrophils and eosinophils was noted (fig. 3). The Van Gieson elastica stain demonstrated some degree of fibrosis. Thus, a subacute to chronic nongranulomatous interstitial inflammation with at least focal criteria of a desquamative interstitial pneumonia (DIP) pattern was diagnosed. With a strong suspicion of an adverse drug reaction, no specific anti-inflammatory therapy (steroids) was introduced, but rather the patient was clinically observed with discontinuation of the ergoline drug, leaving the remainder of the drug regimen unchanged. Clinical recovery was noted within 3 weeks, spontaneous resolution of roentgenological changes confirmed at the 8 and 12 week follow-up evaluation.

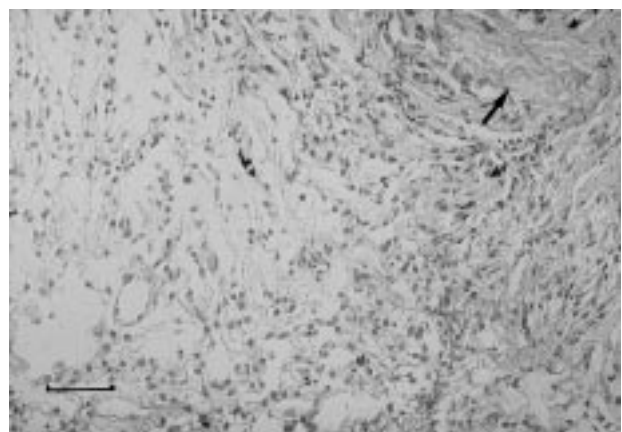


Fig. 3. – Transbronchial biopsy (TBB) taken from the right middle lobe (HE-stain) with mononuclear interstitial infiltration, and some neutrophils and eosinophils. In addition (right upper position), as also certified by Van Gieson staining some degree of focal fibrosis was present (arrow). (Internal scale bar=50 μm .)

Discussion

This case report first of all raises the issue of distinguishing convincingly an immunological from an infectious aetiology. While it certainly appears difficult to definitely rule out atypical pneumonia, the bulk of clinical as well as laboratory evidence points towards a drug-induced interstitial pneumonitis with at least focal characteristics of desquamative interstitial pneumonitis (DIP). In summary, the points favoring this assumption are: 1) a slow nonspecific clinical onset pattern; 2) the widespread bilateral extension of lesions; 3) nonresponsiveness to antibiotic treatment including macrolides; 4) only a moderately elevated CRP level; 5) a predominantly lymphocytic (rather than neutrophilic) alveolitis-type lung lesion; 6) no serological evidence of a current infection with relevant organisms; and 7) no evidence of an active intrinsic systemic immunological disorder as well as an extrinsic air-borne alveolitis.

A number of synthetic dopamin agonists including ergotamine, mesulergine, lisuride, bromocriptine and its congener methysergid are known to be potentially associated with pleuropulmonary disease but also with mediastinal and retroperitoneal fibrosis [1, 2, 5, 6]. Cabergoline, a dopaminergic agent available since 1985 has been more recently identified as an additional cause, although only four cases with pleuropulmonary lesions have been reported [1, 4]. Ergot compounds have a tetracyclic chemical structure in common, believed to be responsible for adverse reactions, since these have never been reported in alternative dopamin agonists such as the disproportionately more frequently prescribed levodopa [6].

The pathogenesis of adverse reactions remains obscure. One potential mechanism could be related to an altered serotonergic receptor function, since most of these agents have a serotonin receptor affinity [7]. Mesothelial cells appear the principal target of the fibrogenic potential of these drugs. Adverse effects have been previously considered to be to some extent dose-related, but clinical disease to low dose bromocriptine has been reported as well [2, 3, 8]. The overall incidence of symptomatic pleuropulmonary reactions to ergolines in general is given as 2–5% of patients, while that of cabergoline in particular is 0.9% of all patients treated with the drug [5]. After withdrawal of the drug, the clinical course is usually benign, resulting in at least partial reversal of lesions, although some degree of fibrosis may definitively persist [2]. However, in one reported cabergoline case, even temporary progression was observed, believed to be related to the extreme long acting profile of the drug [4]. The review of the literature shows that pleural involvement in ergoline induced disease is far more common than pneumonitis and appears the main feature of the disease [9–11]. In comparison, pulmonary involvement is less frequent and less documented. In one major review, the proportion of pneumonitis within the bromocriptine-related respiratory disease variety was given with 43.2% [2], whereas all of the reported cabergoline cases, besides pleuritic changes, appear to have had pulmonary infiltrates [2, 4, 6].

To the authors' knowledge, an interstitial inflammatory lung lesion in the absence of pleuritis has not been explicitly described in cabergoline-related pleuropulmonary disease. Circumstantial evidence in this case suggests a link to the ergoline regimen of the patient, although the administered dose was low. The nature of the observed lesions remains unclear. A hypersensitivity-type immunogenesis rather than toxicity might be assumed on the basis of clinical observations and the low dose given, which is supported by the BAL findings. Whether the HLA-B-27-positive status of the patient, a haplotype potentially associated with an abnormal immune response, may have provided a facilitating and enhancing background for the adverse lung reaction remains only subject to speculation.

In conclusion, these observations suggest that lone pulmonary reactions even to low dose cabergoline treatment may occur, as has been previously reported with a few other ergolines.

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