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Pleural disease during treatment with bromocriptine in patients previously exposed to asbestos

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Pleural disease during treatment with bromocriptine in patients previously exposed to asbestos. G. Hillerdal, J. Lee, A. Blomkvist, A. Rask-Andersen, M. Uddenfeldt, H. Koyi, E. Rasmussen. ©ERS Journals Ltd 1997.

ABSTRACT: Bromocriptine, which is used in the treatment of Parkinson's disease, can cause adverse pleuropulmonary reactions. Exposure to asbestos can result in similar lesions.

Fifteen patients with former exposure to asbestos, who developed pleural fibrosis after treatment with bromocriptine, were observed independently in Sweden (11 patients) and Australia (four patients).

The patients complained of malaise, often associated with weight loss, dyspnoea, and a disturbing cough. Laboratory values included increased erythrocyte sedimentation rate and a low haemoglobin level. Lung function tests showed a restrictive lung function defect. Chest radiographs showed bilateral pleural fibrosis, with small amounts of fluid in some cases. Soon after bromocriptine was withdrawn, the patients improved clinically, and the laboratory values returned to normal. However, in most cases, pleural fibrosis and a restrictive lung function defect persisted to some extent.

In conclusion, in patients who develop pleuropulmonary fibrosis whilst being treated with bromocriptine, former exposure to asbestos should be investigated. Conversely, when pleural changes develop in a patient on bromocriptine and with prior exposure to asbestos, the possible causative role of the drug should be discussed. Special follow-up may be indicated when bromocriptine is planned in a patient with previous asbestos exposure, and if symptoms or signs of pleural fibrosis develop, bromocriptine withdrawal should be considered.

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Bromocriptine, a semisynthetetic ergot alkaloid derivative, acts as a dopamine agonist [1]. The drug has been successfully used for the treatment of Parkinson's disease and prolactinoma. In 1981, RINNE [2] reported that, out of 123 patients on long-term therapy with this drug, seven had developed pleuropulmonary reactions. Since then, to our knowledge, 30 cases of bromocriptine-induced adverse reactions in the lung and/or pleura have been reported in the literature [3–18]. Interestingly, ergot alkaloids other than bromocriptine can cause similar lesions in the chest [19].

Occupational exposure to asbestos is another well-known cause of pleural and lung disease. The pleural lesions are of various types [20]. One form, the diffuse pleural fibrosis, is less common but more severe, in terms of restrictive lung disease, than simple pleural plaques. This pattern is clinically and radiologically similar to the adverse reactions from bromocriptine.

When a patient formerly exposed to asbestos happens to develop Parkinson's disease, is treated with bromocriptine, and develops diffuse pleural thickening, an interesting differential diagnosis is raised, After having seen 15 patients with this particular association, we would like to report on these cases and suggest that there may be a synergistic effect between these two factors. In other words, the risk of adverse respiratory effects from bromocriptine may be enhanced in persons who have previously been exposed to asbestos [21].

For editorial comment see page 2695

Materials and methods

All patients were reviewed if they had been referred to or evaluated by one of the authors during the period 1986–1997 because of restrictive lung function defect caused by pleural and/or pleural-parenchymal lesions, and had been exposed to asbestos in the past and were being treated with bromocriptine. Eleven patients were seen in Sweden and four in the Sydney region of Australia. No attempts were made to recruit other patients in a systematic fashion, nor was an epidemiological study performed among patients treated with bromocriptine or in cohorts of subjects formerly exposed to asbestos. Clinical and laboratory data, such as the erythrocyte sedimentation rate (ESR) and haemoglobin concentration, were tabulated.

A chest radiograph was available for review in each patient, and a computed tomography (CT) scan was

available in 10 cases. Lung function tests were performed in 10 cases, but in five patients with severe symptoms from their Parkinson's disease, even simple tests could not be performed. Bronchoalveolar lavage (BAL) was performed in two patients, as described elsewhere [22].

Once the diagnosis was established, bromocriptine was withdrawn, and the patient was followed-up.

Results

Symptoms and signs

The patients usually presented after a period of up to 6 months with malaise; their other main complaints were dyspnoea on exertion and a troublesome cough. Weight loss was a common finding, and a number of patients had been extensively investigated for suspicion of malignancy by general practitioners or internists.

Laboratory values

An increased ESR was found in 10 of the 11 patients for whom data were available (table 1), and a low haemoglobin level was seen in all cases. There were also other nonspecific laboratory findings compatible with ongoing inflammation, such as an increased platelet count, or immunoglobulins A and G (IgA and IgG), and a high level of C-reactive protein (CRP).

Bronchoalveolar lavage

A BAL was performed in only two cases, and yielded normal results.

Radiology

Chest radiographs showed diffuse bilateral pleural thickening in all patients (figs. 1 and 2). In six patients, pleural fluid was present at some stage of the disease, and, in four cases, thoracocentesis yielded a small-to-moderate amount of fluid (30–300 mL) containing inflammatory cells, with a predominance of lymphocytes (actual percentages unavailable). On the CT scan, there was pleural thickening/fibrosis in all cases, but, usually, no evidence of parenchymal fibrosis was seen. Rounded atelectasis (fig. 1a) was seen in five of the 15 patients.

Lung function tests

Dynamic spirometry was available in 12 patients, and showed a low forced vital capacity (FVC) (mean±SEM) 62±3% predicted (range 50–81% pred). Static spirometry was available in eight cases and showed a restrictive pattern: total lung capacity (TLC) averaged 66±2% pred (range 58–73% pred) and residual volume (RV) averaged 80±6% pred (range 61–109% pred).

Histology

In five patients, pleural biopsy were performed (one by thoracotomy and four *via* a needle biopsy). All biopsies showed extensive nonspecific fibrosis.

Follow-up

Follow-up ranged 1–8 yrs, except in the two most recent cases, which were seen in 1997. After withdrawal of the drug, clinical symptoms, such as cough and malaise, disappeared after a few days, and the laboratory values (including ESR and haemoglobin) level returned to normal after periods ranging from a few weeks to 2 months. Lung function improved only slightly, or remained unchanged, and a restrictive lung function defect often remained due to pleural fibrosis. Case No. 14 is a typical example, as described below. His FVC was 5.0 L (96% pred) before treatment with bromocriptine, dropped to 3.0 L (62% pred) under treatment with the drug, and returned to 3.5 L (71% pred) after the drug was stopped.

Table 1. – Characteristics of the patients studied

Pt No.	Age when seen yrs	Age on asbestos exposure yrs	Occupation	Bromocriptine		ESR when seen	ESR after drug withdrawn	Comments
				mg·day^{-1}	yrs			
1	66	20–60	Building worker	20	5	60	15	Plaques
2	66	19–59	Building worker	20	4	45	15	Plaques
3	66	22–58	Building painter	5	10	65	14	Plaques
4	62	20–57	Building worker	20	5	80	14	Plaques
5	60	18–33	Chemical factory	20	4	117	5	Also asthma
6	77	40–47	Chemical factory	7.5	8	80	-	Plaques
7	79	20–65	Retail*	17.5	5	95	-	Plaques
8	70	45–46	Farmer#	30	5	100	-	Badly restrictive, now on oxygen
9	64	20–57	Building painter	15–20	7	9	7	Plaques
10	75	20–50	Chemical engineer‡	30	1.5	-	-	Plaques
11	68	-	Builder	20	1.5	-	-	Plaques
14	54	20–34	Electrician	10	8	90	13	
15	60	18–36	Building worker	30	10	90	-	

Pt: patient; ESR: erythrocyte sedimentation rate; Plaques: plaques known before pleural fibrosis. *: worked in a hardware store where asbestos was cut, mixed and sold; #: frequently constructed barns *etc.* using asbestos; ‡: worked in an asbestos mine. Patients 12 and 13 not included since exact exposure data are missing.

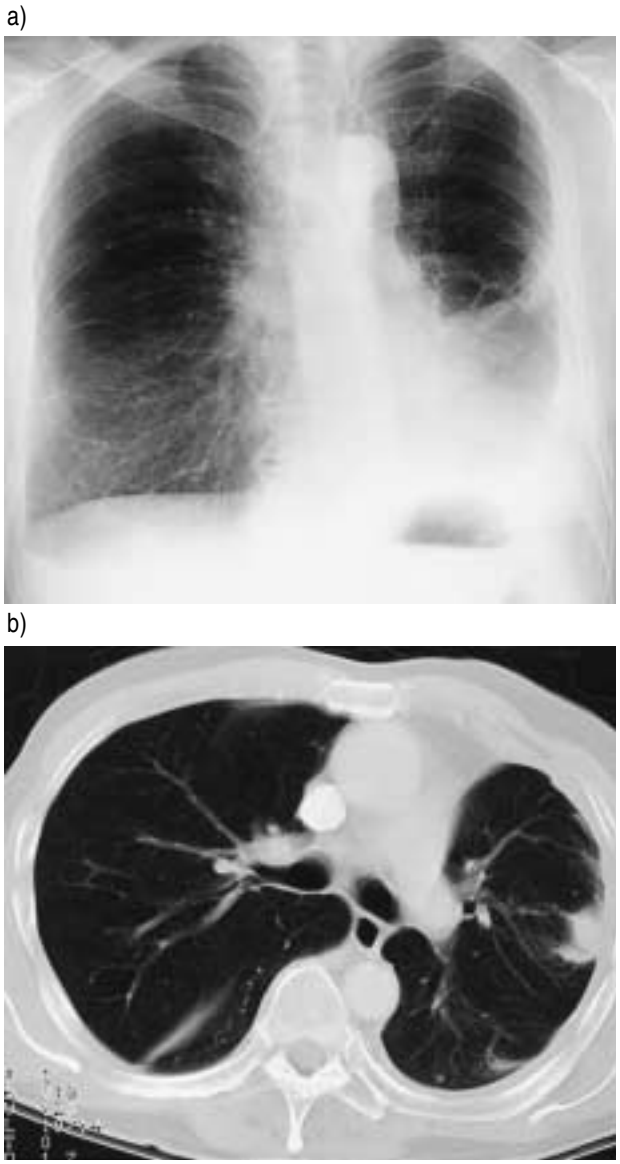

Fig. 1. – a) Chest radiograph of patient No. 9, frontal view. Bilateral pleural thickening is visible, more advanced on the left side where there is a small amount of pleural fluid and a rounded atelectasis. b) Computed tomography scan of patient No. 9, showing small round left-sided atelectasis.

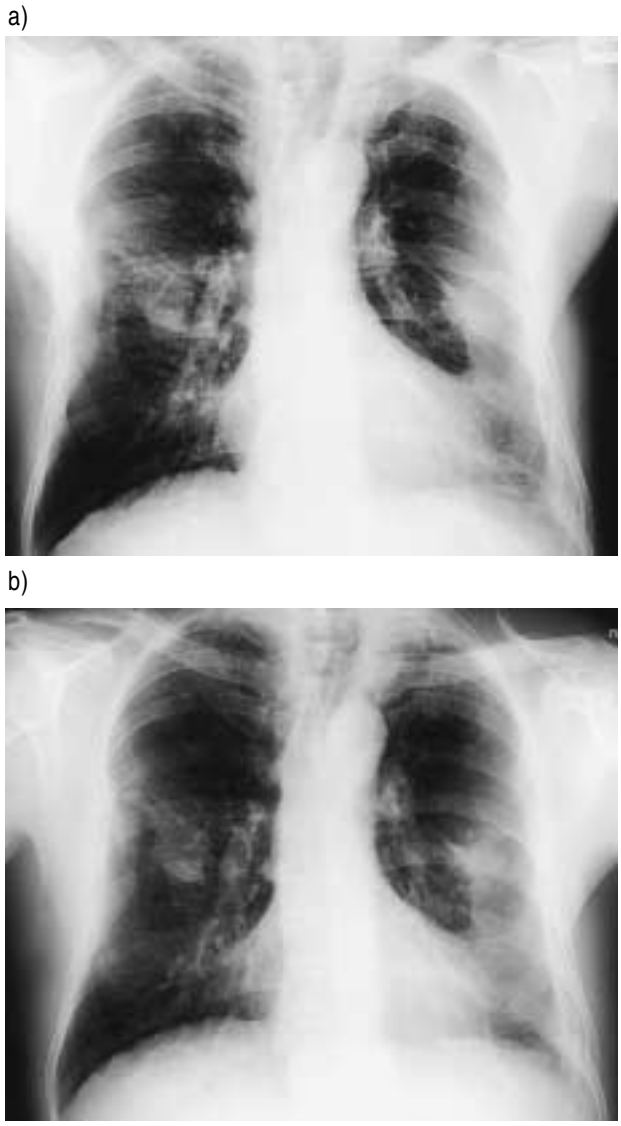

Fig. 2. – Chest radiographs of patient No. 15, frontal view. a) At presentation: extensive plaques are seen on the right side, and diffuse pleural thickening on the left side, together with bilateral rounded atelectasis. b) Two months after withdrawal of bromocriptine: there is a small improvement, but extensive pleural fibrosis remains.

Illustrative case reports

Case No. 9

This man was referred to the Department of Lung Medicine, Karolinska Hospital, Stockholm, Sweden at 64 yrs of age because of bilateral lung lesions. He was a nonsmoker and had been working in the building industry with direct and indirect exposure to asbestos for 37 yrs. In 1985, a chest radiograph showed bilateral pleural plaques. He had been suffering from Parkinson's disease for 8 yrs, and had been treated with bromocriptine, 20 mg·day^{-1}, for the past 5 yrs. Approximately 6 months before referral, he noticed a dry cough and increasing tiredness. He had lost a few kilograms in weight, but his main problem was increasing dyspnoea.

Laboratory tests showed an ESR of 80 mm·h^{-1}, and a haemoglobin level of 105 g·L^{-1}. The chest radiograph showed bilateral pleural lesions, with the left side predominantly affected, and some fluid was present. A thoracocentesis yielded 30 mL of yellowish fluid; and cytology showed a predominance of lymphocytes. A CT scan confirmed that the lesions were mainly pleural, and there was a small amount of fluid (fig. 1). Spirometry showed TLC 68% pred, and vital capacity (VC) 50% pred. Bronchoscopy was normal. A needle biopsy showed a fibrotic and thickened pleura but no malignant cells.

Bromocriptine was withdrawn and, 2 months later, the patient no longer suffered from cough, had regained his original weight and felt much better, but dyspnoea was little improved. Laboratory values were back to normal. The chest radiograph no longer showed fluid, but pleural thickening remained nearly unchanged.

Case No. 14

The patient was referred at 54 yrs of age to the Department of Occupational Medicine in Uppsala, Sweden, for suspicion of asbestosis. He had been working as an electrician in a mine since his teenage years, and had used asbestos for insulation purposes from the start and until he was 36 yrs old. He had been followed with spirometry and chest radiographs sporadically. In 1991, when 49 yrs of age, he had a normal chest radiograph, his VC was 5.0 L (96% pred), and he weighed 85 kg.

At 46 yrs of age, the first symptoms of Parkinson's disease were recorded. One year later, bromocriptine was prescribed, at a dosage of 2.5 mg *t.i.d.*, and the dose was gradually increased to 15 mg·day^{-1}. The patient was in good health and back to full-time work, with a good control of his Parkinson's disease. However, in the summer of 1996, at 53 yrs of age, he felt tired and had to restrict his normal activities. In August 1996, his FVC had fallen to 3.0 L (62% pred). The ESR was 90 mm·h^{-1}, and the haemoglobin level was 127 g·L^{-1}. In December 1996, his haemoglobin level was 118 g·L^{-1}, thrombocytosis was present and serum albumin was 29 g·L^{-1}. The patient's weight was down to 70 kg.

Bromocriptine was withdrawn, and, within 1 week, the patient felt better. Two months later, the ESR was 13 mm·h^{-1}, the haemoglobin value 143 g·L^{-1}, and VC was modestly increased to 3.5 L (71% pred). The patient had regained some weight and, though still dyspnoeic on exertion, he had resumed his normal activities.

Case No. 15

This 60 yr old man was a former building worker and had worked with asbestos for almost 20 yrs. He had never smoked. Parkinson's disease was diagnosed at the age of 42 yrs and, due to gradual worsening of his symptoms, bromocriptine was prescribed at 50 yrs of age, with a final dosage of 30 mg·day^{-1}. The patient was referred to the Lung Department in Gävle (Sweden) for evaluation of bilateral lesions on the chest radiograph. During the last 3–4 months, he had felt tired and increasingly dyspnoeic during exercise, and also complained of a dry irritating cough. The ESR was 90 mm·h^{-1}, haemoglobin 119 g·L^{-1}, and CRP 58 mg·L^{-1}. A chest radiograph showed extensive bilateral pleural fibrosis with some fluid (fig. 2a). In order to rule out pleural mesothelioma, pleural needle biopsies were performed on three different occasions. All showed extensive fibrosis without malignancy.

Bromocriptine was withdrawn, and, 2 days later, the cough had disappeared. Two months later, there was a slight decrease in pleural lesions (fig. 2b), but pleural fibrosis remained. The laboratory values were back to normal.

Discussion

The first report on adverse respiratory effects due to bromocriptine was that by RINNE [2] in 1981, who reported that, out of 123 patients treated with the drug, seven developed pleuroparenchymal lesions. In fact, adverse fibrogenic effects from the drug seem more unusual in clinical practice than once suggested, and it has even been claimed that there is no significant overrepresentation of pleural lesions in patients treated with bromocriptine as compared to controls [23]. In addition to the original article by RINNE [2], 16 further reports comprising 30 patients overall have so far been published (table 2). The pleuropulmonary reaction to ergot drugs is usually a restrictive lung function defect, presumably due to extensive pleural fibrosis [19]. Increased ESR and a low haemoglobin level are also present, together with general malaise and loss of weight [19]. Pleural effusion with various amounts of fluid may also occur [3, 5, 7, 10, 11, 15, 16, 19].

The pleural lesions caused by asbestos are more common than those due to bromocriptine. For instance, in Nordic countries, the incidence of pleural plaques in males aged ≥40 yrs ranges 2–7% [24–27]. Pleural plaques do not usually cause a significant restrictive defect, or only a mild one. A less common asbestos-related manifestation is a diffuse pleural fibrosis, which can cause severe restrictive disease [20]. In the latter form of asbestos-induced pleural involvement, signs of inflammation, such as an increased ESR, have been described in serum, but generalized malaise is usually lacking [28]. As part of this pattern, acute or chronic pleurisies with various amounts of fluid, may also develop in asbestos workers.

How then, to differentiate between asbestos-related and bromocriptine-induced pleural disease in a given patient? The best way is probably to withdraw the drug in all suspected cases. If the general condition of the

Table 2. – Case reports of bromocriptine lung and pleural reactions from the literature

[Ref.]	Sex	Pts n	Age yrs	Bromocriptine mg·day^{-1}	Asbestos exposure
[2]	M	1	61	80–100	ND
[3]	M	1	44	50	ND
[4]	M	1	56	62	Unknown (1)
[5]	M	1	46	60	Asbestos exposure 25 yrs
[6]	M	4	61–66	50	3 unknown (2) 1 asbestos exposure (3)
[7]	M	1	55	20	Asbestos exposure (4)
[8]	M	1	64	30–40	ND
[9]	M	8	57–68	6–50	ND
[10]	M	4	60–73	15–40	ND
[11]	M	1	72	30	ND
[12]	M	2	58, 79	15, 30	ND
[13]	M	1	63	30	ND
[14]	F	1	68	20	ND
[15]	M	1	64	35	Asbestos exposure (5)
[16]	M	1	42	10	Asbestos exposure (6)
[17]	M	1	66	10–15	ND, denied asbestos exposure

ND: not determined (no occupational history given); Pts: patients; M: male; F: female. The following occupational histories were given: (1) electrical engineer, no mention of asbestos; (2) electrical industry, no mention of asbestos; (3) automechanic; (4) machine operator; (5) goldsmith; (6) occupation not given.

patients improves, the cough and general malaise disappear and the laboratory values normalize, then the case can probably be considered to be drug-related. As a consequence, further use of bromocriptine should be avoided. There are currently no data to indicate whether cross-sensitivity exists between bromocriptine and other ergot akaloids [19, 21]. Furthermore, we believe that caution should be exercised when prescribing bromocriptine to a patient known to have previous exposure to asbestos, because the risk of developing pleural lesions may be enhanced. Moreover, patients on bromocriptine, especially those with prior asbestos exposure, should be followed-up at regular intervals as regards the development of respiratory symptoms and/or signs of pleural fibrosis. If such signs develop, bromocriptine should be withdrawn, and other anti-Parkinson's disease drugs should be considered.

Our study does not provide epidemiological proof that asbestos potentiates the adverse effects of bromocriptine or other ergot alkaloids. An occupational history was given in only a few of the previous reports on ergot-induced respiratory dysfunction (table 2). Of the 30 previously reported cases, no occupational history was reported in 21, and, of the remaining nine, five had been exposed to asbestos, while one was unexposed, and for three, the exposure was not clearly stated. Since the main exposure to asbestos occurred in industrialized countries in the 1960s and 1970s, an increasing number of previously exposed workers now reach the age at which Parkinson's disease may be seen. If an association exists between former exposure to asbestos and the risk of developing pleural disease upon exposure to bromocriptine, as suggested by our work, then an increasing incidence of such adverse effects may be expected to develop in the future.

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