

Early Pleuropulmonary Toxicity Associated With Cabergoline, an Antiparkinsonian Drug

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We report a case of pleural effusion, pericardial thickening, and pulmonary involvement in a patient with dry cough, dyspnea, edema, and changes in the skin of the lower limbs. Treatment with cabergoline (Sogilen) had been started 4 months earlier. Pleural effusion, pericardial thickening, and impaired pulmonary function (airflow obstruction, increased airway resistance, and reduced carbon monoxide diffusing capacity) were observed. The Naranjo scale pointed to a probable relationship between cabergoline and these adverse effects. We report on outcome after 2 months of follow-up, during which time there was a slow and incomplete improvement in respiratory function. This is the first case in our practice setting of early pleuropulmonary toxicity associated with cabergoline.

Key words: *Pleural effusion. Pulmonary toxicity. Cabergoline.*

Toxicidad pleuropulmonar precoz asociada al tratamiento con cabergolina, un fármaco antiparkinsoniano

Describimos un caso de derrame pleural, engrosamiento pericárdico y afectación pulmonar en un paciente con síntomas de tos seca, disnea, edemas y afectación cutánea de extremidades inferiores. Cuatro meses antes había iniciado tratamiento con cabergolina (Sogilen®). Se demostró la existencia de derrame pleural, engrosamiento pericárdico y alteración de las pruebas funcionales respiratorias (obstrucción del flujo aéreo, incremento de la resistencia de las vías aéreas y disminución de la capacidad de transferencia de monóxido de carbono). La escala de Naranjo imputó una relación “probable” entre el fármaco y los efectos adversos detectados. Incluimos la evaluación evolutiva tras 2 meses de seguimiento, durante el cual se documentó una mejoría lenta e incompleta de las alteraciones funcionales respiratorias. En el ámbito de nuestra práctica neumológica, este caso constituye la primera descripción clínica de toxicidad pleuropulmonar precoz asociada al tratamiento con cabergolina.

Palabras clave: *Derrame pleural. Toxicidad pulmonar. Cabergolina.*

Introduction

Pleural effusion is the abnormal accumulation of fluid in the pleural space. In pathophysiologic terms, pleural effusion is the result of an imbalance between the formation of pleural fluid and its reabsorption. In clinical terms, it is always abnormal even though at least 30% of cases are considered idiopathic. Most cases, however, can be explained by processes that are pleuropulmonary or extrapulmonary. The latter include a miscellany of causes

associated with diseases affecting other organs (eg, heart, liver, kidney, or pancreas), connective system diseases (eg, lupus, rheumatoid arthritis), or neoplastic diseases (with or without pleural metastasis). Particularly interesting is evidence that pleural effusion can be precipitated by certain drugs, the most common ones being nitrofurantoin, propranolol, and chemotherapeutic agents (bleomycin, methotrexate, mitomycin, and procarbazine), which may also cause pulmonary toxicity (pneumonitis or fibrosis).¹

Case Description

The patient was a 78-year-old man with no history of smoking or exposure to inhaled organic or inorganic compounds. He was not taking medication and had no known drug allergies. His admission was scheduled for evaluation of a left pleural effusion whose onset was uncertain. He was not under treatment on

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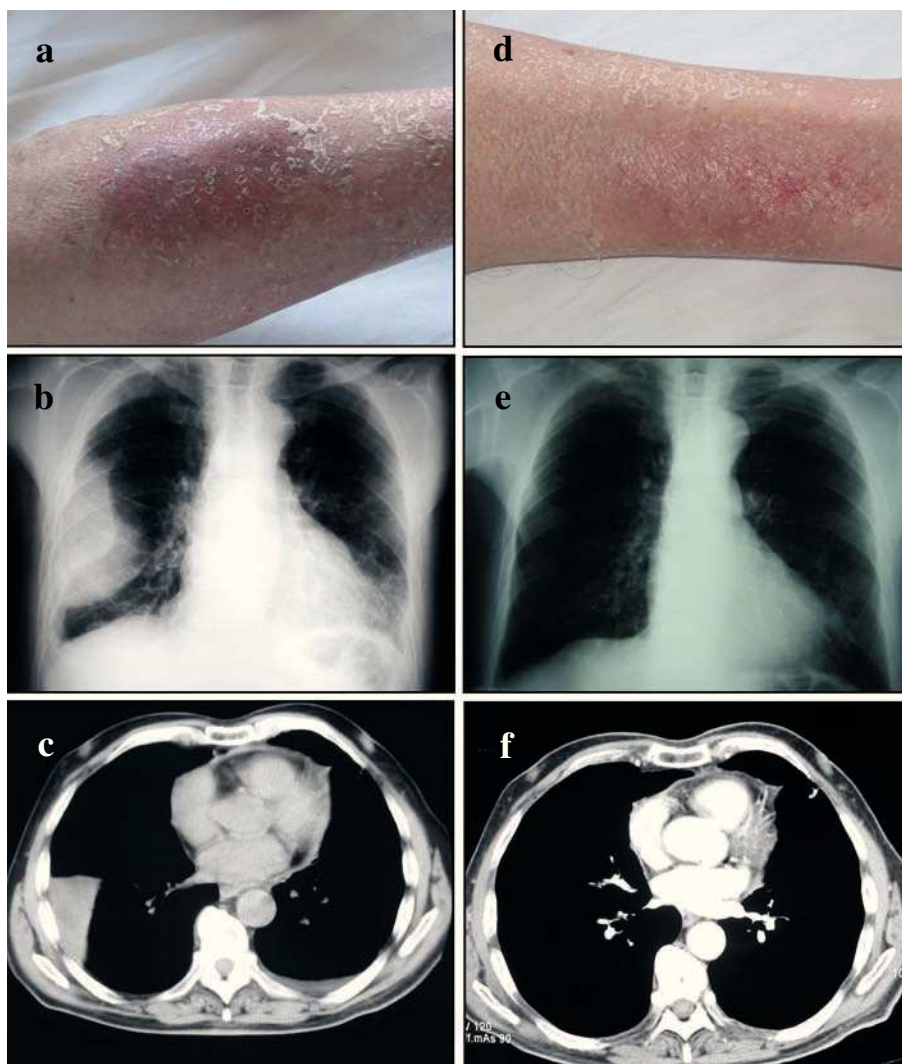


Figure 1. Early (*a-c*) and later (*d-f*) images of some of the most significant aspects of the case, showing a comparison of the skin lesions (*a* and *d*), conventional chest radiograph (posteroanterior projection) (*b* and *e*) and computed tomography scan of the thorax (*c* and *f*). Specific details on the interpretation of these images and explorations can be obtained from the text.

admission (treatment having been suspended by his neurologist). Relevant medical history included assessment for Parkinson disease at another center. The first symptoms, which had appeared 3 months before the patient came to our hospital, took the form of insomnia, headache, asthenia, progressive edema in the lower limbs accompanied by nonpruritic trophic skin changes, dry cough, and progressive dyspnea, even after mild exertion. His neurologist requested a chest radiograph, which revealed the presence of pleural effusion, and the patient was referred to our center for evaluation. Four months earlier he was prescribed oral cabergoline (Sogilen) at 1 mg/d. Between our evaluation and the scheduled admission the patient interrupted this treatment for approximately 1 week. During this period, both the edema and skin lesions improved, and only mild dry cough and less intense dyspnea remained. When the patient was admitted to our center, he was conscious and well oriented to time, place and person, and well hydrated, with normal skin color. His blood pressure was 110/70 mm Hg, heart rate 74 beats/min, and axillary temperature 36°C. The most noticeable sign was a reduction in vesicular sounds in the middle third of the hemithorax, although no adventitious respiratory sounds were noted. The lower limbs showed signs of venous insufficiency, with dystrophic desquamative skin changes (Figure 1a). Stiffness of the neck

and left arm was observed, as was moderate akinesia of the left arm and leg and resting tremor in the left upper limb. Gait and balance were normal.

The chest radiograph (Figure 1b) revealed an opacity in the right lateral and posterior costophrenic sinuses indicating the presence of pleural fluid. A convex bilateral outward-bulging fissure sign was also suggestive of pleural effusion; occupation of the left lateral and posterior costophrenic sinuses were likewise consistent with the presence of a small quantity of pleural fluid in this region. Increased bronchovascular density with peribronchial cuffing attributable to interstitial edema was also observed, along with passive collapse of the base of the right lung. A computed tomography scan of the thorax (Figure 1c) confirmed the presence of right-sided pleural effusion extending into the fissure. Nonspecific lymph node involvement was observed in the right paratracheal and prevascular areas. There was pericardial thickening with no sign of effusion. Slight peribronchial cuffing and thickening of the interlobar septa were evident in the lung parenchyma and attributable to interstitial disease. Spirometric parameters were altered, as was carbon monoxide diffusing capacity (Table).

We felt that, from the clinical point of view, it was reasonable to suspect associated pneumonitis and transitory pleural serositis

Characteristics in Relation to Cabergoline Treatment*

	During Therapy	After Withdrawal of Therapy		
		Early Evaluation	Later Evaluation	Change
Dose of cabergoline, mg/d	1	0	0	
Time since therapy withdrawn, d	0	10	55	
Dyspnea	At rest	Mild exertion	Strenuous exertion	
Radiologic evidence of pleural effusion	Yes	Yes	No	
Respiratory function				
FEV ₁ , mL (% predicted)		1420 (48)	1740 (59)	+23%
FVC, mL (% predicted)		2640 (61)	3310 (77)	+25%
FEV ₁ /FVC, %		54	52	
TLC, mL (% predicted)		5860 (91)	5920 (92)	+1%
RV, mL (% predicted)		3440 (128)	2640 (98)	-30%
RV/TLC, %		59 (133)	45 (101)	-24%
DLCO, mmol/min/kPa (% predicted)		6.01 (72)	7.89 (95)	+23%
KCO, mmol/min/kPa/L (% predicted)		1.38 (96)	1.76 (122)	+28%
6-min walk test				
Baseline SaO ₂ , %		97	98	
Change in SaO ₂ , %		-1%	-1%	
Distance walked, m (% pred.)		378 (82)	513 (112)	+36%

*FEV₁ indicates forced expiratory volume in the first second of expiration; FVC, forced vital capacity; TLC, total lung capacity; RV, residual volume; DLCO, carbon monoxide diffusing capacity; KCO, lung diffusion capacity corrected for alveolar ventilation; SaO₂, arterial oxygen saturation.

as an adverse effect of cabergoline therapy; therefore, we recommended against the continuation or restarting of this treatment in this patient. Inhaled corticosteroids and bronchodilator therapy were prescribed.

Discussion

This report summarizes the presentation of pleural effusion, pericardial thickening, and lung involvement in a patient with no known history of smoking or heart or lung disease who came to our emergency department with subacute symptoms of dyspnea, edema, and cutaneous changes on the lower limbs. Based on application of the scale of Naranjo and colleagues,² this is a case of probable early pleuropulmonary toxicity associated with cabergoline and is the first such case reported.

Cabergoline (C₂₆H₃₇N₅O₂) is a synthetic derivative of ergoline, which acts and is used as a dopamine agonist.³ It was approved by the United States Food and Drug Administration in 1997 and came onto the market in Spain under the name Sogilen in 2001. It is generally indicated for the treatment of hyperprolactinemic alterations (both idiopathic alterations and those related to pituitary adenomas).⁴ Its effect is dose-dependent thanks to its activity as a dopamine D₂ receptor agonist in the anterior pituitary gland. The affinity of other receptors (eg, adrenergic, serotonergic, or histaminergic receptors) for cabergoline is very low. Cabergoline is administered orally and undergoes significant first-pass metabolism after systemic absorption, being extensively metabolized by hydrolysis in the liver, with minimum involvement of microsomal cytochrome P450.⁴ At least 4 metabolites are produced, although none seems to contribute to the drug's mechanism of action.³ Its elimination half-life is approximately 60 hours and its metabolites are eliminated in feces (60% to 70%), although 22% of the dose is eliminated by the kidneys.³

Currently, the main indication for cabergoline is as a treatment for hyperprolactinemia, although it can also be used to treat the motor fluctuations associated with Parkinson disease, where it has proven efficacious when used as monotherapy in the initial phases.⁵ The effective dose is approximately 3 mg/d and the drug can be used as adjuvant therapy with the combination of levodopa and carbidopa in patients with Parkinson disease who suffer from motor fluctuations. Although this combination seems to be safe and efficacious, there may be additional neurological side effects. In fact, hallucinations have been reported when cabergoline and levodopa are combined. The most common side effects of cabergoline are nausea, vomiting, headache, dizziness, constipation, asthenia, abdominal pain, and vertigo. Nausea appears to be the only dose-dependent symptom. The package insert refers to common side effects observed in patients with Parkinson disease who have been treated with cabergoline; these include confusion, dyskinesia, hallucinations, and peripheral edema. Symptoms resolve when the drug is withdrawn.⁶

The present case is not the only one in which an association has been observed between cabergoline and pleuropulmonary effects. The package insert warns of adverse reactions in the respiratory tract, although these are rare,⁷ and recommends that cabergoline be used with caution in patients with underlying lung disease. As with other ergot derivatives, cabergoline has been associated with pleuropulmonary alterations, such as pleural effusion and pulmonary fibrosis.^{6,8-11} A specific search has enabled us to identify only 2 similar clinical descriptions of cabergoline-induced toxicity.^{6,9}

The 3 most noteworthy aspects of the present case are the follow-up period, the respiratory functional evaluation, and the absence of underlying illnesses or of an alternative diagnosis. To our knowledge, this is the first report of cabergoline-induced pleuropulmonary toxicity in Spain.

When the patient came to our emergency department, there was evidence of fluid in the pleural cavity; however, this gradually disappeared when treatment was withdrawn, and no specific therapeutic intervention was necessary (Figure 1e) other than withdrawing the drug. Findings related to pulmonary function included the following: *a*) spirometry indicating increased airway resistance and airflow obstruction, pointing to airway disease even in the absence of a history of smoking, bronchial asthma, or any other disease that would explain the alterations; *b*) reduced carbon monoxide diffusing capacity, indicative of interstitial lung disease; *c*) signs of pleural and pericardial effusion (the latter very small) leading to a suspicion of serositis; *d*) edema in extremities and trophic skin changes coinciding temporarily with functional abnormalities, as has been reported in association with cabergoline⁶ (Figures 1a and 1d); and *e*) complete disappearance of the pleural effusion after drug clearance (Figures 1e and 1f) as well as partial resolution of the respiratory function alterations as evidenced by clinical and functional evaluations during follow-up. As for toxicology, the present report does not enable us to establish a cause-effect relationship between the drug and the cutaneous and pleuropulmonary effects observed. Although this is a potential limitation, carrying out a clinical trial to demonstrate or refute this hypothetical causal relationship is not an alternative. Nevertheless, if we take into account the definitions of Naranjo et al² for estimating the probability of adverse drug reactions, the aforementioned arguments enable us to claim a probable causal relationship between treatment with cabergoline and the patient's symptoms. This evidence led us to report the case to the Toxicology Department of the Spanish National Health Service.

A potential limitation of the present report is the lack of cytochemical analysis of the pleural fluid. During the period between withdrawal of therapy, detection of the case in our emergency room, and admission to hospital, the effusion had almost disappeared completely, thus rendering it impossible to obtain a sample by fine needle aspiration. When the patient stopped taking the medication, both the edema and the respiratory difficulty present at onset resolved spontaneously with no need for further intervention.

Long-term follow-up is necessary to evaluate the possibility that alterations are irreversible after the unusual

toxicity observed in this case. It is impossible to predict the effect of these alterations in patients who, unlike ours, have an underlying heart or lung disease.

To conclude, we believe clinicians should remember that cabergoline can cause pleuropulmonary disease (with or without symptoms) in patients who receive the drug as treatment for hyperprolactinemia or Parkinson disease.

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