severe hemomediastinum, a conservative approach is advocated with correction of the coagulation defect to avoid postoperative complications. 

ML is recorded in about 15% of patients receiving high doses of corticosteroids. 

In Cushing’s disease, steroid-induced lipomatosus has an acute or subacute axial development, often involving the retro-orbital or epidural spaces. ML is usually asymptomatic and fortuitously suspected by the radiologic finding of an enlarged mediastinum. However, lipomatosus may become compressive and may produce cough, dyspnea, or superior vena caval syndrome. The diagnosis is easily confirmed by fatty density on CT scan or MRI. 

Steroid-induced ML syndrome. The diagnosis is easily confirmed by fatty density on CT scan or MRI.7 Steroid-induced ML syndrome. The diagnosis is easily confirmed by fatty density on CT scan or MRI. Steroid-induced ML improves in most patients following decreasing steroid dosage, but surgical decompression of the mediastinum may be necessary in severe forms. In our patient, the recent increase of steroid therapy associated with the development of both exophthalmia and enlarged mediastinum were highly suggestive of steroid-induced lipomatosus, which was confirmed by surgical and pathologic findings. To the best of our knowledge, hemorrhagic complications of ML have never been described. However, fat tissues have dense vascularization, and gastric or colonic lipomatosus has been associated with GI bleeding.

In our patient, the use of LMWH in the context of chronic renal failure likely contributed to mediastinal fat hemorrhage. LMWH should be used very cautiously in patients with renal insufficiency because of an increased risk of hemorrhagic complications, and plasma anti-factor Xa concentrations have to be monitored in such patients.1,2 Although hemomediastinum is an uncommon complication of LMWH therapy, this diagnosis should be suspected in a patient presenting with an enlarged mediastinum and no evidence of aortic dissection. Among the various conditions associated with spontaneous hemomediastinum, ML should be considered in patients receiving long-term, high-dose steroids.

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**Pleuropulmonary Disease Due to Pergolide Use for Restless Legs Syndrome**

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Pergolide is an ergot-derived dopamine agonist used in Parkinson’s disease and, increasingly, in restless legs syndrome. We report a patient with a 2.5-year history of weight loss, pleuropulmonary fibrosis, and exudative pleural effusion that developed insidiously while taking this medication. The extensive and invasive workup that preceded the diagnosis highlights the difficulty in attributing such a process to a drug reaction. This is the second report of such a reaction to pergolide, which is one of the increasing number of ergot-derived compounds in common clinical use. (CHEST 2001; 120:313–316)

Key words: Parkinson’s disease; pergolide; pleuropulmonary fibrosis; restless legs syndrome

Abbreviations: PD = Parkinson’s disease; RLS = restless legs syndrome

The ergot-derived alkaloids comprise a large number of compounds sharing a common ring structure and include several medications frequently used for Parkinson’s disease (PD) and migraine headaches, among others (Table 1). A number of these compounds have been described to produce a pleuropulmonary fibrosis syndrome,1 in addition to retroperitoneal fibrosis.2 The diagnosis of this drug-associated pleuropulmonary fibrosis syndrome is largely one of exclusion and is often made with some difficulty given the presence of coexisting medical problems. It is confirmed by response to withdrawal of the offending agent. Pergolide, an ergot-derived alkaloid, was introduced as an adjunct therapy for PD3 and has subsequently been used with some success for restless legs syndrome (RLS).4 We wish to report a case of pergolide-induced pleuropulmonary fibrosis.

**CASE REPORT**

A 65-year-old white man was transferred to our institution for evaluation of progressive weight loss (50 lb total), increasing dyspnea, and fatigue noted, retrospectively, to have begun > 2 years earlier. Workup that included chest and abdominal CT, barium enema, and sigmoidoscopy had been unrevealing. Six months prior to transfer, the patient was incidentally noted to have a 2.5-year history of weight loss. On examination, he was afebrile, with a BP of 130/66, HR 94, RR 18, and temperature of 98 °F. Significant findings included a right upper lobe pleural effusion and one 2 cm in the left upper lobe. A tentative diagnosis of pleuropulmonary fibrosis was made, with posteroanterior and lateral radiographs of the chest to rule out masses or cavitation. The chest CT scan showed an exudative right upper lobe pleural effusion and one 2 cm in the left upper lobe. Abdominal CT scan showed a normal liver and spleen, with no evidence of masses, aortic dissection, or retroperitoneal fibrosis. A CT pulmonary angiogram was negative for pulmonal emboli. A diagnosis of pleuropulmonary fibrosis was made and the patient was started on treatment with prednisone. He was discharged on prednisone 40 mg/day and was to continue this for 1 month. He was seen in follow-up after 6 weeks and had lost 8 lb. He was then started on prednisone 40 mg/m²/day. He was seen in follow-up after 5 months and had lost an additional 10 lb. He was then started on prednisone 40 mg/m²/day. He was seen in follow-up after 6 months and had lost an additional 10 lb. He was then started on prednisone 40 mg/m²/day. He was seen in follow-up after 6 months and had lost an additional 10 lb.
have a small right pleural effusion. The patient had worsening dyspnea, and serial chest radiographs showed an increasing right pleural effusion. One month prior to transfer, thoracentesis documented an exudative effusion, but neither pleural fluid nor pleural biopsy specimens revealed an etiology. The patient underwent a right thoracoscopy that demonstrated “multiple plaque-like lesions on the chest wall suggestive of a mesothelioma.” Biopsy specimens revealed only fibrous tissue with chronic inflammation, and culture findings were negative. The patient developed fever, worsening dyspnea, and evidence on chest radiograph of a large right hydropneumothorax. Serologic workup prior to transfer included negative results on antinuclear antibodies, antinuclear cytoplasmic antibodies, antiglomerular basement membrane antibodies, cryoglobulins, rapid plasma reagin, and rheumatoid factor studies, as well as normal complement levels (C3 and C4), serum, and urine protein electrophoresis.

The patient’s medical history was notable for RLS for nearly 30 years, as well as noninsulin-dependent diabetes mellitus, hypertension, and arteriosclerotic cerebral vascular disease. His medications included pergolide, 3.5 mg/d; glipizide, 20 mg/d; losartan, 25 mg once daily; and warfarin, 5 mg once daily. The pergolide was begun 3 years earlier for treatment of RLS at the recommended starting dose of 0.05 mg qd and gradually titrated upward. Social history was notable for an 8 pack-year history of tobacco use in the 1950s and for 3 months of possible asbestos exposure in 1948 while working in a warehouse unloading asbestos pipe sleeves.

On transfer to our institution, the physical examination was remarkable for a respiratory rate of 28 breaths/min on 3 L of oxygen via nasal cannula. The patient was cachectic. Lung examination revealed dullness to percussion in the lower half of the right lung field, with decreased breath sounds in the lower half of the right lung and at the left base. Laboratory data showed a WBC count of 19.6 × 10^9/L (90% segmented neutrophils, 2% lymphocytes, 5% monocytes, and 1% eosinophils); chemistry panel showed an albumin of 2.6 g/dL (reference, 3.5 to 5.3 g/dL). Urinalysis revealed no proteinuria. Chest radiograph (Fig 1, top) showed a loculated right hydropneumothorax. Thoracentesis revealed bloody fluid with pH of 7.45, lactate dehydrogenase of 590 mg/dL, and protein of 5.1 g/dL. Cytology showed no evidence of malignancy. Purified protein derivative findings were negative.

The patient underwent bronchoscopy with transbronchial lung biopsy that showed focal intra-alveolar fibrin and no evidence of fungal forms or malignancy. BAL showed mild inflammation with reactive epithelial cells. The patient then underwent right open lung and pleural biopsy that revealed a peel surrounding the lung, and multiple white thickened plaques on the diaphragm and the mediastinal surface. Final pathology findings revealed chronic inflammation with no evidence of malignancy or asbestos-related changes.

**Table 1—Ergot Derivatives and Their Common Indications**

<table>
<thead>
<tr>
<th>Derivatives</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bromocriptine</td>
<td>Hyperprolactinemia, PD, acromegaly</td>
</tr>
<tr>
<td>Dihydroergotamine</td>
<td>Migraine headache, deep venous thrombosis and pulmonary embolus prophylaxis</td>
</tr>
<tr>
<td>Ergoloid mesylates</td>
<td>Age-related decline in mental status</td>
</tr>
<tr>
<td>Ergotamine</td>
<td>Migraine headache</td>
</tr>
<tr>
<td>Ergonovine</td>
<td>Postpartum and postabortion hemorrhage</td>
</tr>
<tr>
<td>Methylergonovine</td>
<td>Postpartum and postabortion hemorrhage</td>
</tr>
<tr>
<td>Methysergide</td>
<td>Migraine headache, carcinoid-related diarrhea, narcolepsy</td>
</tr>
<tr>
<td>Pergolide</td>
<td>PD, RLS</td>
</tr>
</tbody>
</table>

*Table includes medications commonly prescribed in the United States. Other medications that have been reported to cause pleuropulmonary fibrosis but are not currently available in the United States include cabergoline and nicergoline.*
term medications were maintained. Pergolide treatment was discontinued and all other long-term medications were maintained.

In light of multiple studies with negative findings for malignancy and infection, alternative causes of fibrosis, pleural thickening, and exudative effusions were sought. Pergolide was considered as a causative agent and treatment was discontinued. The patient was treated with a 2-week course of corticosteroids given the inflammation present on biopsy specimens. Within several weeks, the patient had significant subjective and objective improvement in his dyspnea and exertional capacity (Table 2). The patient had significant subjective and objective improvement in his dyspnea and exertional capacity (Table 2). The patient was now 3 years from the discontinuation of this medication and with dramatic improvements in chest radiography (Fig 1, bottom) and pulmonary function testing (Table 2).

**DISCUSSION**

The differential diagnosis of an exudative effusion in a patient with this history includes occult malignancy, infection (eg, tuberculosis), benign asbestos pleural effusion, and drug reaction. The patient underwent an extensive evaluation including a pleural biopsy, bronchoscopy with transbronchial biopsy, thoracoscopic and open lung biopsies, as well as multiple thoracenteses. None of these studies documented malignancy or infection. Tuberculosis seemed unlikely given the negative findings on purified protein derivative and multiple cultures. The patient had a history of a short exposure to asbestos, but had no pleural plaques and no asbestos bodies on biopsy. While this does not exclude benign asbestos pleural disease, his systemic symptoms of weight loss and malaise as well as the absence of chest wall pain in his presentation contrast with the typical presentation. In addition, benign asbestos pleural effusions usually occur within 10 to 15 years of asbestos exposure. Ultimately, the diagnosis of pergolide-associated pleuropulmonary fibrosis is based on the response to the removal of the offending agent. In this patient, only pergolide treatment was discontinued and all other long-term medications were maintained.

When this patient was evaluated, there were no reports of such reactions to pergolide; however, there were reports of pleuropulmonary disease associated with other ergot derivatives. Subsequently a single case report of pergolide-associated pleuropulmonary disease has been reported. Pergolide has been described to cause retroperitoneal fibrosis, which is also associated with ergot derivatives.

The first report of pleuropulmonary disease attributed to ergot derivatives was a case series in 1966 that described 27 patients receiving methysergide who developed retroperitoneal fibrosis. Two of the patients developed pleural and pulmonary inflammation and fibrosis. An additional reported patient underwent a lung biopsy revealing “fibrosis around vessels and terminal bronchioles.” Clinically, all three patients had episodes of pleural inflammation with friction rubs, fever, and pleural effusions. In each case, symptoms resolved with discontinuation of methysergide treatment. A similar syndrome has been reported with bromocriptine, other dopamine agonists, and ergotamines. Pleuropulmonary involvement in eight patients receiving ergot derivatives other than bromocriptine was also reviewed. The patterns of involvement in this series included a spectrum from interstitial pneumonitis to pleuropulmonary fibrosis with associated exudative effusions. The mean age of the patients was 70 years, with a treatment duration of 8 months to 15 years. Clinical and radiographic changes were very similar to those noted in this case. Similarly, patients in all reported series underwent extensive evaluations for malignancy and infection before suspicion was directed toward medications.

The mechanism by which the ergot derivatives produce fibrosis, either pleuropulmonary or retroperitoneal, remains obscure. There is no evidence that it is dependent on dosage or duration of use of the medication. Some questions have been raised as to whether this represents a serotonergic effect of these medications, as serotonin has been shown to be profibrotic. It is this serotonergic effect that was implicated in the valvular abnormalities associated with the use of phenteramine-fenfluramine and in the carcinoid syndrome. The relevance of this mechanism to pleuropulmonary fibrosis has yet to be proved. The causal relation between the ergots and this syndrome seems quite well established, however, with multiple cases showing regression of symptoms with withdrawal of the offending agent and, in a few instances, recurrence of symptoms when the patient was rechallenged.

We report this case to draw attention to a large class of compounds, the ergot-derived alkaloids (Table 1), which are used in treatment of a growing number of diseases. The pleuropulmonary syndrome associated with their use appears to be induced by many of these compounds. The pulmonary symptoms develop insidiously, making the association with onset of use of this medication difficult. The constitutional nature of the syndrome leads to its confusion with malignancy (particularly mesothelioma) and infection. The rapid clinical improvement that results from discontinuation of the medication confirms the diagnosis.

**REFERENCES**

A solitary lung mass is a very rare thoracic presentation of sarcoidosis.1 When pulmonary sarcoidosis requires treatment, systemic corticosteroids are usually effective.2 We report a case of pulmonary sarcoidosis that presented as a left lung mass that was refractory to treatment with oral corticosteroids. Transthoracic injection of corticosteroids under CT guidance was effective in reducing the size of the lung lesion and improving symptoms.

CASE REPORT

A 38-year-old white woman presented with left-sided anterior pleuritic chest pain (duration, 3 months). Pulmonary sarcoidosis had been diagnosed using bronchoscopy with transbronchial biopsy 5 years previously. The patient had no known history of beryllium exposure, and all bronchoscopy specimens were negative for mycobacteria and fungi. She had received treatment with prednisone for 3 years, and this had been discontinued 2 years prior to presentation. She had no history, signs, or symptoms of extrapulmonary sarcoidosis.

She was examined by her local physician, who requested a chest radiograph and prescribed antibiotics for presumed pneumonia. Neither her pleuritic chest pain nor the lung lesion on chest radiograph improved. She was then prescribed prednisone, 40 mg/d, without significant improvement over 2 months. She was referred to our medical center.

She denied fever, night sweats, weight loss, hemoptysis, or any constitutional symptoms. She remained active and in excellent physical condition, other than left-sided pleuritic chest pain. She was a lifelong nonsmoker, had no history of tuberculosis, and had several negative tuberculosis skin test results. Physical examination revealed a mildly obese, mildly cushingoid, healthy-appearing white woman. Vital signs were normal. There was tenderness to compression over the left anterior chest wall. Spirometry revealed a mild restrictive ventilatory defect that was unchanged from spirometry performed 4 years previously. A chest radiograph (Fig 1) showed a normal mediastinum and a left upper lung mass.

A transthoracic core needle biopsy of the left lung lesion revealed noncaseating granuloma. The specimen was negative for mycobacteria and fungi, and revealed no crystals by polarized light examination. The patient was prescribed prednisone, 60 mg/d for 1 month, without any significant change in the lung mass on chest radiograph; there was no improvement in her chest pain. Chest CT scan (Fig 2, top) revealed a 4 × 7-cm left upper lobe mass extending to the anterior pleural surface.

A CT fluoroscopy-guided transthoracic needle injection of dexamethasone, 32 mg, into the lesion was performed under local anesthesia and IV conscious sedation. Three 23-gage needles were introduced percutaneously at three different levels of the lesion. Approximately 10 to 11 mg of dexamethasone were injected into each site. No significant pain or discomfort was produced by the injection. The patient was kept overnight in the hospital for observation. Six weeks later, the patient returned and noted significant improvement in her pleuritic chest pain. Repeat chest CT scan (Fig 2, bottom) performed 2 months after injection revealed a dramatic reduction in the size of the left lung lesion.

**FIGURE 1.** Chest radiograph at presentation showing a left lung mass.