Retroperitoneal fibrosis caused by pergolide in a patient with Parkinson’s disease

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ABSTRACT

Retroperitoneal fibrosis (RPF) is an uncommon disorder that may cause ureteric obstruction with renal damage. Pergolide, a dopaminergic agonist used in the treatment of Parkinson’s disease, has rarely been related to the development of RPF. We report on a 78-year-old woman with Parkinson’s disease who presented with hydroureteronephrosis and developed RPF and serosal fibrosis during treatment with pergolide. Following discontinuation of pergolide therapy and placement of a double-J stent, her renal function improved. Inflammatory markers returned to normal limits within two months and the retroperitoneal fibrotic mass became smaller.

INTRODUCTION

Retroperitoneal fibrosis (RPF) is a rare disease which may result in obstructive uropathy and renal failure. The disease may be idiopathic or secondary. More than two thirds of patients with RPF have idiopathic RPF. RPF associated with drugs has been especially described with the ergot derivatives methysergide and bromocriptine. Pergolide is also an ergot derivative dopaminergic agonist commonly used in the treatment of Parkinson’s disease (PD). RPF secondary to pergolide is very rare, but has previously been reported. We describe a case of RPF associated with pergolide use in a patient with PD and have reviewed literature.
lymphadenomegaly was found. She was afebrile and had mild pretibial oedema. There were signs of Parkinson’s disease on neurological examination.

The results of her initial laboratory examination were as follows: BUN 14.4 mmol/l, creatinine 250 µmol/l, glucose normal, sodium 143 mmol/l, potassium 5.1 mmol/l, uric acid 0.25 mmol/l, ALT 20 IU/l, AST 33 IU/l, LDH 526 IU/l, alkaline phosphatase 214 IU/l, total protein 7.6 g/l, albumin 3.6 g/l, erythrocyte sedimentation rate (ESR) 94 mm/h, C-reactive protein (CRP) 37.6 mg/l, total bilirubin normal, total cholesterol 3.9 mmol/l, triglyceride 0.73 mmol/l, intact parathyroid hormone 60.6 pg/ml (12-72), white blood cell 5.9 x 10⁹/l, haematocrit (Hct) 0.29 l/l, platelets 285 x 10⁹/l, iron 10.4 µmol/l, total iron binding capacity 45.4 µmol/l and ferritin 601.5 ng/ml. Urine analysis revealed a urine density of 1012, protein negative, pH 5, three erythrocytes and 13 leucocytes per high-power field. The daily urine volume was approximately 1200 ml. Glomerular filtration rate (GFR) was 8.8 ml/min. Hepatitis B and C serology, and anti-HIV were negative.

Chest X-ray showed bilateral mild pleural effusion in the lower zones of lungs and electrocardiography was normal except for incomplete left bundle branch block. Computed tomography (CT) of the thorax revealed minimal bilateral pleural effusion, thickening of pleura and mild peri-cardial effusion. Echocardiography suggested 50% ejection fraction, minimal pericardial effusion and mild thickening of pericardium. Because of a pleural effusion, thoracentesis was performed. The results of the pleural fluid proved to be exudate. Bacteria and acid-fast bacilli were not detected, and polymerase chain reaction assay for tuberculosis was negative. Fluid culture was also negative. Cytological examination of pleural fluid showed no malignant cells, but there were some fibroblasts. Pleural biopsy could not be performed due to minimal pleural effusion. Abdomen and pelvic CT scans revealed bilateral hydroureteronephrosis, a presacral soft tissue mass measuring 2 cm at the widest location and extending bilaterally to the pelvic wall. Based on these findings, bilateral double-J stents were inserted; BUN and creatinine decreased gradually and her symptoms improved. Pelvic magnetic resonance imaging (MRI) showed presacral mature and immature fibrotic tissue which was hypointense in T₁ weighted and hyperintense in T₂ weighted images, and that measured 1.7 cm at the widest location (figure 1). This tissue extended to the 5th lumbar spine vertebrae. A diagnosis of RPF was made. A true-cut biopsy was carried out for excluding malignancy. Histopathological examination revealed no evidence of malignancy, but fibroadipose tissue was seen. After exclusion of other possible causes, RPF was attributed to pergolide therapy and the pergolide was discontinued. Pericardial and pleural thickening were thought to be associated with fibrosis due to pergolide. MRI angiography was planned for detecting a possible constriction of a major vessel, but was not performed due to the hazardous effect of the contrast agent on renal function. Doppler ultrasonography of the lower extremities revealed no thrombii. Two months later, control pelvic MRI showed reduction in fibrotic tissue that now measured 1.1 cm (figure 2), serum ESR and CRP levels had decreased and GFR increased to 27 ml/min. Because of her age and the risk of osteoporosis, we decided not to treat with corticosteroids or immunosuppressive drugs. After a follow-up of four months, the patient’s ESR was 30 mm/h, CRP was 3.1 mg/l, BUN 11.5 mmol/l and creatinine were 120 µmol/l.

DISCUSSION

An aetiology of RPF is detected in only about one third of the patients. Secondary causes of RPF include drugs such as ergot derivatives, infections (such as HIV or tuberculosis),
haemorrhage, malignancy and aortic aneurysm.\textsuperscript{1,2,11,12} Associations with connective tissue diseases, including ankylosing spondylitis, systemic lupus erythematosus, polyarteritis nodosa and Wegener granulomatosis have been previously reported. In addition, HLA-B27 may be positive in some cases.\textsuperscript{12-14} In our patient ANA and HLA-B27 were negative and anticardiolipin antibodies were within the normal range. Laboratory results showed elevated ESR and CRP and normochromic normocytic anaemia. An elevated ESR has been reported in 80 to 90\% of cases of RPF.\textsuperscript{2,8,12,15} Therefore, ESR and CRP may be used for follow-up of such patients. The best diagnostic tests for RPF are imaging methods. CT is the most frequently used method. Although MRI provides separation of RPF from muscle or adipose tissue compared with CT, its superiority has not been established.\textsuperscript{16,17} We made the diagnosis of RPF based on CT and MRI findings. A biopsy was then performed and RPF diagnosis was confirmed by histopathological findings. The necessity of laparoscopic or open biopsies has been emphasised to exclude malignancy and establish other causes of secondary RPF by some authors.\textsuperscript{2,12} On the other hand, malignant areas may be missed with both laparoscopic and open biopsy. Either CT or ultrasonographic-guided percutaneous needle biopsy should be carried out in each case of diagnostic doubt\textsuperscript{2,12} to exclude malignancy, infection and other causes of secondary RPF. Our patient had had Parkinson’s disease for 13 years and she had been taking pergolide since 1999. Pergolide is a dopaminergic agonist and RPF associated with this drug has been previously recognised in five cases according to the English medical literature (table 1).\textsuperscript{6-10} Pergolide-induced RPF is the most probable diagnosis in our patient because of lack of other secondary causes. Although in the five other reported cases, the RPF had a typical location, our case involved the presacral region, an atypical site. RPF typically involves soft tissue mass, surrounding the ureters, kidney and vascular structure.\textsuperscript{11,12} Pergolide-induced RPF usually occurs on average two years after the initiation of pergolide.\textsuperscript{8,10} In our patient, initial symptoms started in the fourth year of treatment. Pergolide therapy was discontinued in all reported patients. Only one patient (case 1) was treated with corticosteroids. Ureteric stents were inserted in four of the cases. In addition, two patients (cases 2 and 3) were treated surgically. The clinical features and management of pergolide-induced RPF patients are summarised in table 1. Serosal fibrosis related to pergolide has been documented,\textsuperscript{8,18} but in these cases, serosal fibrosis and RPF occurred separately. Further, we detected a simultaneous occurrence of pleural and pericardial fibrosis and RPF in our patient. The mechanism of RPF caused by ergot derivatives, such as bromocriptine and pergolide, is not entirely understood, but an idiosyncratic immune response associated with the drug, which acts as a hapten, is considered to be the causative mechanism of RPF. In addition, mononuclear cell infiltrations have been reported in biopsy specimens.\textsuperscript{8,19} However, the mechanism of RPF associated with methysergide differs from the other ergot alkaloids. Methysergide behaves as a serotonin antagonist and a prolonged intake of this drug causes rebound release of serotonin. There is a profibrotic effect of serotonin and this might be responsible for the development of RPF.\textsuperscript{12,20} Because of these findings, corticosteroids are effectively used for suppressing the inflammation, especially in the early stages.\textsuperscript{1,11,14} The trials of other treatment modalities

<table>
<thead>
<tr>
<th>CASE</th>
<th>AGE/SEX</th>
<th>TIME INTERVAL*</th>
<th>LOCATION</th>
<th>SEVERITY OF DISEASE</th>
<th>OTHER MANIFESTATIONS OF FIBROSIS</th>
<th>TREATMENT**</th>
<th>RESPONSE TO TREATMENT</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>61/M</td>
<td>24 months</td>
<td>Typical</td>
<td>Mild RF, left H, EE</td>
<td>-</td>
<td>Corticosteroid 20 mg/day</td>
<td>Successful</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>68/F</td>
<td>24 months</td>
<td>Typical</td>
<td>Severe RF, bilateral H, anaemia</td>
<td>-</td>
<td>Ureterolysis and omental wrap</td>
<td>Successful</td>
<td>7</td>
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<tr>
<td>3</td>
<td>68/F</td>
<td>28 months</td>
<td>Typical</td>
<td>Severe RF, left H, EE</td>
<td>-</td>
<td>Surgical removal of mass, US</td>
<td>Successful</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>83/F</td>
<td>19 months</td>
<td>Typical</td>
<td>Severe RF, bilateral H</td>
<td>-</td>
<td>US</td>
<td>Successful</td>
<td>10</td>
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<tr>
<td>5</td>
<td>63/F</td>
<td>21 months</td>
<td>Typical</td>
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<td>-</td>
<td>Nephrostomy, US</td>
<td>Successful</td>
<td>9</td>
</tr>
<tr>
<td>6</td>
<td>78/F</td>
<td>48 months</td>
<td>Atypical</td>
<td>Mild RF, bilateral H, EE, anaemia</td>
<td>Pericardial and pleural fibrosis</td>
<td>US</td>
<td>Successful</td>
<td>This report</td>
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*Time interval between the start of pergolide and development of symptoms and/or the diagnosis of RPF. **Pergolide was discontinued in all patients. RF = renal failure, H = hydronephrosis/hydroureretonephrosis, EE = elevated erythrocyt sedimentation rate, US = ureteric stent.

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Bilici, et al. Retroperitoneal fibrosis caused by pergolide.
in RPF such surgery, tamoxifen and immunosuppressive drugs have been documented in some cases.21,22 After pergolide therapy was discontinued, the pelvic MRI showed a reduction in the fibrotic mass, and serum ESR and CRP decreased. Therefore, she was left untreated and a follow-up was decided.

This patient is a rare case of RPF and possible pleural-pericardial fibrosis caused by pergolide. In patients with Parkinson’s disease who receive pergolide, renal function, ESR and CRP levels should be closely checked. RPF should particularly be considered in the differential diagnosis of elevated ESR, CRP and disturbance of renal function in patients with Parkinson’s disease treated with pergolide. ESR and CRP levels are important for both diagnosis and response to treatment in these patients.

REFERENCES