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CASE REPORT

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

A. Bilici[1*], B. Karadag[1], A. Doventas[1], D. Suna Erdincler[1], S. Cetinkaya[2], G. Ogut[2], V. Tezcan[1], T. Beger[1]

[1]Department of Internal Medicine, Division of Geriatrics and [2]Department of Radiology, Cerrahpasa School of Medicine, Istanbul University, Istanbul, Turkey, tel.: +90 212-633 23 63, fax: +90 212-530 74 40, e-mail: ahmetknower@softhome.net, *corresponding author

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.[1,2] RPF associated with drugs and has been especially described with the ergot derivatives methysergide and bromocriptine.[3,4] Pergolide is also an ergot derivative dopaminergic agonist commonly used in the treatment of Parkinson's disease (PD).[5] RPF secondary to pergolide is very rare, but has previously been reported.[6-10] We describe a case of RPF associated with pergolide use in a patient with PD and have reviewed literature.

CASE REPORT

A 78-year-old woman, who was found to have Parkinson's disease in 1990 at the age of 65, was initially treated with levodopa/benserazide (50/12.5 mg orally, three times a day). Bromocriptine was added in 1991 and selegiline in 1993 because of increasing parkinsonian symptoms. Her symptoms worsened and tremor increased under this treatment. A stereotaxic neurosurgical intervention was performed to the thalamus and pergolide treatment was started in 1999; bromocriptine and selegiline were stopped while levodopa/benserazide was continued. With pergolide therapy, her parkinsonian symptoms improved and the pergolide was increased gradually to 3 mg/day.

She had a history of hypertension, which had been well controlled for two years with amlodipine 5 mg/day orally. Four months ago, swelling and erythema of her left leg developed and was treated with warfarin 5 mg/day orally for deep venous thrombosis, but treatment was stopped within five days because of diffuse ecchymoses. Doppler ultrasonography was not undertaken. Her swelling and erythema decreased spontaneously. She was then admitted with complaints of low back pain, pretibial oedema, nausea, vomiting and anorexia which had started two months ago. High titres of serum blood urea nitrogen (BUN) and creatinine were detected in biochemical testing and urinary ultrasonography revealed bilateral hydroureteronephrosis. With these findings she was transferred to our hospital. On examination, she was pale, her blood pressure was 130/80 mmHg, with a pulse of 88 beats/min and her heart sounds and jugular venous pressure were normal. There was a 2/6 systolic murmur at the apex. Her breathing sounds were normal except for mildly decreased sounds in the lower zones of both lungs. No organomegaly or

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 10^9/l, haematocrit (Hct) 0.29 l/l, platelets 285 x 10^9/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 pericardial 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. Cytopathological 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 T_2 weighted and hyperintense in T_1 weighted images, and that measured 1.7 cm at the widest location (*figure 1*). This tissue extended to the 5th lumber 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 ultrasono-graphy of the lower extremities revealed no thrombi. 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),

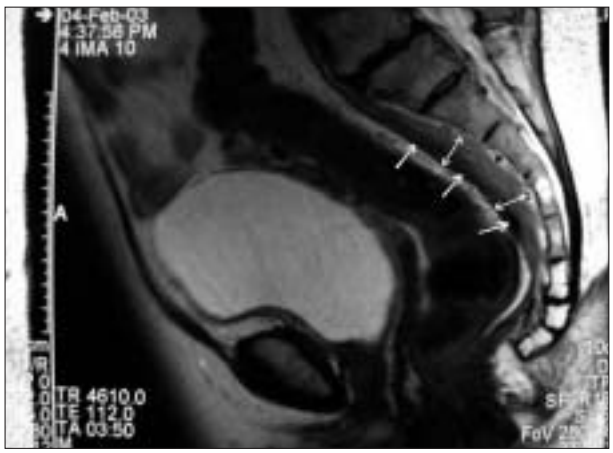

Figure 1
Sagital T_2 weighted MRI images depict a presacral soft tissue of heterogenous intensity

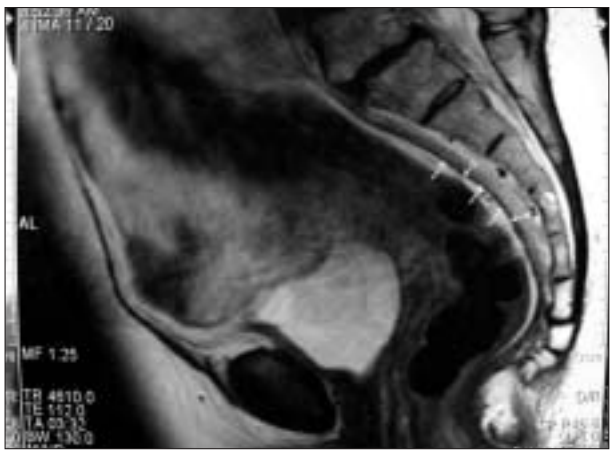

Figure 2
Two months later control MRI examination showed that the soft tissue had regressed in size

haemorrhage, malignancy and aortic aneurysm.[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.[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.[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.[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.[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[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*).[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.[11,12] Pergolide-induced RPF usually occurs on average two years after the initiation of pergolide.[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,[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.[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.[12,20] Because of these findings, corticosteroids are effectively used for suppressing the inflammation, especially in the early stages.[2,11,14] The trials of other treatment modalities

Table 1
The clinical features and management of pergolide-induced RPF patients

CASE	AGE/SEX	TIME INTERVAL*	LOCATION	SEVERITY OF DISEASE	OTHER MANIFESTATIONS OF FIBROSIS	TREATMENT**	RESPONSE TO TREATMENT	REFERENCE
1	61/M	24 months	Typical	Mild RF, left H, EE	-	Corticosteroid 20 mg/day	Successful	8
2	68/F	24 months	Typical	Severe RF, bilateral H, anaemia	-	Ureterolysis and omental wrap	Successful	7
3	68/F	28 months	Typical	Severe RF, left H, EE	-	Surgical removal of mass, US	Successful	6
4	83/F	19 months	Typical	Severe RF, bilateral H	-	US	Successful	10
5	63/F	21 months	Typical	Severe RF, bilateral H, anaemia	-	Nephrostomy, US	Successful	9
6	78/F	48 months	Atypical	Mild RF, bilateral H, EE, anaemia	Pericardial and pleural fibrosis	US	Successful	This report

**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/hydroureteronephrosis, EE = elevated erythrocyt sedimentation rate, US = ureteric stent.*

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.

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