Retroperitoneal Fibrosis With Periaortic and Pericardial Involvement

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A 66-year old man, who had been diagnosed with dilated cardiomyopathy and felt a progressive shortness of breath and fatigability, was admitted to hospital. Computed tomography showed a thickening of the aortic wall from the aortic arch to the aortic bifurcation, as well as mild pleural and pericardial effusion. Intravenous pyelography showed severe ureteral stenosis, along with hydronephrosis, of the left side. There was a marked increase in C-reactive protein and the erythrocyte sedimentation rate, but the serology for connective tissue disease and perinuclear antineutrophil cytoplasmic antibodies was negative. Retroperitoneal fibrosis (RPF) with intrathoracic extension was diagnosed. After confirming the absence of malignant disease, an oral prednisolone treatment of 30 mg/day was started, and this ameliorated the ureteral obstruction, aortic wall thickening and pericardial effusion. The patient had been taking 300 mg of loxoprofen sodium for headaches every day for 16 years. The relationship between loxoprofen, cardiomyopathy and RPF remains unclear. There is a possibility of RPF in the patients with a thickening of thoracic aortic wall, as in this case.

Key Words: Analgesic drugs; Cardiomyopathy; Fibrosis; Pericardial effusion

Case Report

A 66-year old man with a 6-month history of dull lower-back pain and shortness of breath was admitted to our hospital (University of Tokyo Graduate School of Medicine). Twelve years before this admission, he had been admitted under the diagnosis of advanced atrioventricular block and had a pacemaker implanted. At that time, ultrasonography showed a dilated left ventricular diameter with diffusely decreased left ventricular contraction. A coronary artery angiography showed no significant stenosis. Despite extensive examination, sarcoidosis, amyloidosis, collagen vascular disease or endocrine disorders were not found, and thus idiopathic dilated cardiomyopathy (DCM) was diagnosed. He had a family history of diabetes, hypertension and cerebral infarction. Notably, he had been taking 300 mg of loxoprofen sodium for headaches every day for the past 16 years.

On admission, his blood pressure was 150/70 mmHg. Distension of the jugular vein was not detected. His lungs were clear and cardiac examination did not reveal a murmur. Abdominal examination showed slight distension of the left back, suggesting enlargement the left kidney. There were no palpable enlarged superficial lymph nodes.

The results to following investigations were obtained: hemoglobin 11.2 g/dl; creatinine 0.86 mg/dl; urea 18.0 mg/dl; C-reactive protein (CRP) 5.24 mg/dl; erythrocyte sedimentation rate (ESR) 106 mm/h; brain-type natriuretic peptide (BNP) 185.2 pg/ml; normal liver function tests, negative serology for anti-nuclear antigen; and normal urinalysis. Perinuclear antineutrophil cytoplasmic antibody (P-ANCA) test was negative.

A chest radiograph showed a slightly enlarged cardiac silhouette. Cardiac ultrasonography indicated an end-diastolic left ventricular diameter of 69 mm, an ejection fraction of 36%, mild pericardial thickening and a small amount of pericardial effusion. Abdominal ultrasonography disclosed left-side hydronephrosis. Computed tomography (CT) indicated thickening of the aortic wall between the aortic arch and the aortic bifurcation (Fig 1). A small amount of pleural and pericardial effusion was noted. A bulky fibrotic mass was found around the aorta, extending from the diaphragm to the aortic bifurcation. Excretory urography showed no excretion of the contrast medium from the left kidney (Fig 2). After his admission, the patient’s renal function deteriorated, with serum creatinine levels of 1.41 mg/dl at 1 month after admission. Neither the chest and abdominal CT scan nor endoscopic examination of the upper and lower gastrointestinal tracts showed evidence of malignancy. On the basis of these findings, RPF was diagnosed. After initiating daily prednisolone treatment at 30 mg per os, the dull lower-back pain was gradually relieved, although the shortness of breath was unchanged. After the
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Circulation Journal   Vol.69, June 2005

Fig 1. Computed tomography scan of the patient's abdomen. (A) Thickening of the descending thoracic aortic wall. (B) Periaortic retroperitoneal mass. The mass is enhanced inhomogeneously by the contrast medium, suggesting the presence of active inflammation. (C) Intraluminal thrombi with ulcerative projections (arrows).

Fig 2. Excretory urography showing no excretion of the contrast medium from the left kidney.

Fig 3. Computed tomography scan of the patient's abdomen without enhancement by the contrast medium. (A) Before the steroid therapy, the aortic wall (arrows) appears thickened. (B) Two months after initiating the steroid therapy, the thickness of the aortic wall (arrows) is markedly decreased.

Patient was discharged, a follow-up CT performed at the outpatient department, which showed a decrease in peri-toneal mass, as well as in the amount of pleural and pericardial effusion and in aortic wall thickness (Fig 3). Serum creatinine levels gradually decreased to the normal range.

Discussion

RPF is characterized by replacement of the normal tissue of the retroperitoneum with fibrosis and/or chronic inflammation. Although RPF is a rather uncommon disease (1/2,000,000), it has been diagnosed with increasing frequency since the advent of CT and magnetic resonance imaging. Although the cause of RPF remains uncertain, a systemic immunological and/or autoimmune base is suspected. Approximately two-thirds of cases are considered to be idiopathic, and the remaining third are presumably ascribed to other causes, such as analgesic drug medication, abdominal aortic aneurysm and malignant tumors. The fibrosis occasionally causes an encasement of retroperitoneal structures, leading to hydronephrosis and progressive renal failure. On rare occasions, RPF might coexist with mediastinal fibrosis, which leads to pericardial involvement, resulting in a constrictive pericarditis. Other possible cardiovascular involvement might include periaortitis obstruction of the mesenteric arteries and inferior vena cava, and venous thrombosis. Our patient complained of easy fatigability in the course of dilated cardiomyopathy. His plasma BNP levels were found to be elevated; however, they had not changed markedly over the previous year (177 pg/ml 11 months before this admission). Therefore, the fatigue and shortness of breath in this patient might be due to RPF.
Pericardial and pleural effusion and thickening of the aortic wall were observed in this case. The P-ANCA was negative; however, the thickening of the aortic wall thickening coupled with elevated ESR and CRP resembles aortitis. It is known that periarterial inflammation can associate with RPF. Although the clinical presentations are different, RPF and inflammatory abdominal aortic aneurysm might be encompassed by chronic periaortitis because their histopathological characteristics are identical. In fact, vasculitis in different sized arteries, including the aorta and its major branches, has been reported to coexist with RPF.\(^\text{10,11}\)

Two months after the initiation of the steroid treatment, the thickening of the aortic wall was markedly reduced. Similar time course has been reported by Nakamura et al.\(^\text{12}\) In their report, they showed the presence of inflammation as well as fibrosis histologically. In our case, a biopsy of the periaortic mass had not been taken. However, as the thickness of aortic wall reduced rather promptly after the steroid treatment, it is possible that perivascular inflammation, in addition to organic fibrosis, might have played a role in the aortic wall thickening.\(^\text{12}\)

Our patient had been taking loxoprofen sodium inappropriately for a prolonged period for headaches. Several drugs have been implicated in the pathogenesis of RPF, because RPF is reversible on their discontinuation. Among these drugs, methysergide and other ergot alkyloids, which are used to treat headaches, are most commonly associated with RPF.\(^\text{13}\) Other drugs that have been implicated include pergolide, \(\beta\)-blockers, methyldopa, phenacetin and hydralazine. Until now, however, there have been no reports of a possible association between loxoprofen sodium and RPF. Nevertheless, the pathophysiology of drug-induced RPF is not known, and it has been suggested that the drug itself might act as a hapten, and non steroidal anti-inflammatory drugs (NSAIDs) might induce arteritis.\(^\text{14}\) Therefore, the possibility remains that there is a relationship between loxoprofen sodium abuse and RPF in the present case.

The present case had initially been diagnosed as DCM. Whether there was any pathophysiological association between cardiomyopathy and RPF in the present case remains unclear. Some systemic diseases, such as Erdheim–Chester disease, might cause both RPF and severe cardiomyopathy. Thus, the clinical course of this patient should also be carefully followed.\(^\text{15,16}\)

In summary, we have reported a patient with DCM who experienced RPF with pleural, pericardial, and periaortic involvement. Prednisolone treatment reduced the periarterial thickening and bulky mass that had been obstructing the left side urinary tract. The possible association between NSAID abuse and RPF remains an issue for future consideration.

### References