Mitral Stenosis in Pseudoxanthoma Elasticum*

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A 54-year-old woman with pseudoxanthoma elasticum presented with tight mitral stenosis with thickened and restricted mitral valve leaflets. She initially revealed systemic hypertension and moderate mitral regurgitation due to mitral valve prolapse. One year after the start of treatment for hypertension, thickening of the mitral valve gradually progressed and she showed tight mitral stenosis without regurgitation. It was considered that another differential diagnosis must be added to the uncommon causes of mitral stenosis.

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Pseudoxanthoma elasticum is an inherited disorder of the connective tissue with major involvement of the skin,1 eyes, and gastrointestinal and cardiovascular systems.2 The clinical cardiovascular manifestation includes peripheral vascular disease, hypertension, coronary artery disease, restriction to filling due to subendocardial fibrosis with congestive heart failure,3 and the clinical manifestations of prolapse of the mitral valve.4 In this article, however, we report a case of pseudoxanthoma elasticum that revealed clinical features resembling mitral stenosis with the thickened and restricted mitral valve leaflets.

CASE REPORT

A 54-year-old woman was referred to Keio University Hospital because of hypertension that had been noted in her third decade. Her parents were blood relations. She had no history of rheumatic fever. She had complained of visual impairment in the second decade, and intermittent claudication in the fourth decade. She had a severe melena at the age of 41 years old, and paroxysmal nocturnal dyspnea at 43 years of age.

Physical examination revealed decreased pulse and atrophic changes in radial, dorsal pedal, and postero-tibial arteries, blood pressure of 210/110 mm Hg in both arms, a clear pulmonary field, no hepatosplenomegaly, and no symptom of congestion. Thickened, coarse, and grooved skin resembling "peau d'orange," which had appeared in the second decade, was found in the neck, axillae, abdomen, and inguinal folds. On cardiac auscultation, the first heart sound was accentuated, and a systolic regurgitant murmur (Levine 2/6) was noted at the apex. Echocardiography revealed a thickened mitral valve with prolapse of the anterior leaflet. Chamber size and wall motion of the left ventricle were within normal range. Color flow mapping revealed moderate regurgitant flow into the left atrium.

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FIGURE 1. Histologic condition of skin biopsy specimen. In the middle and lower layers of the dermis, the elastic fibers appear swollen and irregularly clumped (elastic fiber stain, original magnification ×100).

The patient was diagnosed as having pseudoxanthoma elasticum from the above findings, and the hypertension was treated with a calcium blocker (diltiazem) and an angiotensin-converting enzyme inhibitor (enalapril). One year later, when the blood pressure was decreased to 120/70 mm Hg, she was admitted to the hospital for evaluation of cardiovascular involvement. Interestingly, physical examination revealed a diastolic rumbling murmur (Levine 2/6) at the apex with an opening snap of the mitral valve. No systolic regurgitant murmur was heard. Laboratory data showed normal complete blood cell counts, and normal hepatorenal function. The plasma renin activity was slightly elevated (3.2 ng/mL/h; normal range, 0.9 to 2.4) and the plasma concentration of aldosterone was within normal range. Retinography demonstrated angiod streaks,

FIGURE 2. Two-dimensional echocardiography of the short-axis view at the fourth left sternal border. The thickened, calcified stenotic valve leaflets are shown. Note that fusion of the mitral commissure is not prominent in comparison with rheumatic mitral stenosis.
discoid regions, and chorioretinitis. Biopsy specimen of the axillary skin (Fig 1) showed swollen and clumped elastic fibers in the dermis. Electrocardiography showed a normal sinus rhythm with a rate of 80 beats per minute with frequent multifocal supraventricular premature beats. Chest roentgenogram showed mild cardiomegaly with a cardiothoracic ratio of 55 percent, and double contrast of the slightly enlarged left atrium with a thick calcification of the mitral valve. Echocardiography (Fig 2) revealed thickened, calcified stenotic mitral valve leaflets and poor leaflet separation in diastole. The leaflet failed to close in mid-diastole and possibly does not reopen widely during atrial contraction. The motion of the anterior and posterior valve leaflets was severely restricted. Moreover, pannus of the leaflet and fusion of the valve commissure were not observed, indicating that the body of the mitral leaflet was less compliant due to fibrotic changes. The mitral valve orifice area measured by two-dimensional echocardiography and pulsed Doppler echocardiography was 1.0 cm². Peak pressure gradient during diastole calculated by transmitral flow showed 21 mm Hg. Color flow mapping revealed no mitral regurgitation.

Cardiac catheterization revealed an elevated pulmonary wedge pressure of 19 mm Hg with a mean diastolic transmural pressure gradient of 18.2 mm Hg. The right ventricular and pulmonary arterial systolic pressure were 48 and 44 mm Hg, respectively. Cardiac output by thermodilution was 5.3 L/min (3.4 L/min/m²). Mitral valve area was calculated as 1.1 cm² using Gorlin's equation. Coronary arteriography showed no significant stenosis. Left ventriculography revealed no mitral regurgitation and a normal-sized left ventricle of 73 ml/m² with a slightly depressed motion of the apical wall. Myocardial biopsy specimen of the right ventricle revealed that the endocardium was prominently thickened with elastic fibers (Fig 3). Mild myocardial hypertrophy was also observed. There were no Aschoff nodules or fibrous triangular scars of the healed Aschoff nodules, which are characteristic of rheumatic heart disease. No damaged myocardial fibers, fatty degeneration, or vacuolation due to rheumatic myocarditis was observed. These findings are not direct proof but strongly suggest that the mitral valve is impaired with the proliferation of elastic fibers. Thus, tight mitral stenosis with pseudoxanthoma elasticum was diagnosed in this patient.

**DISCUSSION**

Previous studies have revealed that cardiac involvement of pseudoxanthoma elasticum include coronary artery disease, subendocardial fibrosis, and invasion of the cardiac valves. Mitral and aortic valves are typically invaded, and mitral regurgitation due to mitral prolapse can be observed. However, whether it directly involves the mitral valve and causes significant mitral stenosis has not been clarified. The association of pseudoxanthoma elasticum and mitral stenosis was reported by Coffman and Sommers in 1959. They showed the pathologic changes of the mitral valve in a necropsy case, and suggested that the degeneration of elastic fibers, disorganization with fragmentation and clumping, and calcification of elastic fibers might cause mitral stenosis. To date and to our knowledge, no other case of mitral stenosis with pseudoxanthoma elasticum has been reported. The present case appears to be a very rare case that demonstrates the natural course of the mitral stenosis in pseudoxanthoma elasticum.

The present patient has some clinical features and findings that are not characteristic of rheumatic mitral valve disease. One such feature is the rapid progression from mitral regurgitation to mitral stenosis within a year, and another is the specific echocardiographic findings. The alteration from mitral regurgitation to mitral stenosis was partially caused by afterload reduction, but the primary factor was probably the progression of the thickening and restriction of the mitral valve. Both the present patient and the patient whose case was previously reported survived more than 50 years, although it is well known that early death may occur from hemorrhage, congestive heart failure, myocardial infarction, and cerebrovascular accidents. The clinical course of the present patient may suggest that mitral stenosis in a patient with pseudoxanthoma elasticum is caused by an advanced form of the mitral valve prolapse.

The echocardiographic findings of the present patient differed somewhat from the findings in rheumatic valve disease. Of the anterior mitral leaflet, which is characteristic of rheumatic mitral stenosis, was not demonstrated, and the anterior mitral leaflet moved like a door. Hence, the body of the valve leaflet seemed to be less compliant and severely restricted. Moreover, there was little fusion of the commissure of both leaflets, and only slight thickening of the subvalvular apparatus. These findings indicate a difference in the genesis of the degeneration of elastic fibers of the valve leaflets and the fusion of the mitral apparatus.

The uncommon genesis of the mitral stenosis was known to be due to the various disease processes. Pseudoxanthoma elasticum should be considered one of the uncommon causes of mitral stenosis.

**REFERENCES**


**FIGURE 3.** Histologic condition of the myocardial biopsy specimen of the right ventricle. Endocardium is prominently thickened with elastic fibers. Mild myocardial hypertrophy was observed (elastic fiber stain, original magnification ×100).