Pseudoxanthoma elasticum exhibiting heart failure associated with severe mitral valve regurgitation: a case report

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Background: Pseudoxanthoma elasticum (PXE) is a rare inherited systemic disease of connective tissue that primarily affects the skin, retina, and cardiovascular system due to mutations in the ATP-binding cassette subfamily C member 6 (*ABCC6*) gene. The etiology of heart failure in this rare condition might be associated with a variety of situations, including coronary artery disease, valvular disease, and cardiomyopathy. Although cardiovascular complications can be life-threatening and require surgical intervention, there is often a delay in seeking medical attention until serious complication occurs among patients with PXE.

Case Description: A 63-year-old male was admitted to our hospital with dyspnea. Prior to admission, he had been diagnosed as having PXE at 56 years of age, based on the presence of visual impairment and yellow papules around the neck that pathologically revealed degeneration and fragmentation of the elastic fibers. Upon admission, chest X-ray showed pulmonary edema and bilateral pleural effusion. Transthoracic echocardiography showed severe mitral valve regurgitation. The severity of mitral valve regurgitation did not improve substantially after medical treatment, which indicated the need for surgical intervention. He underwent mitral annuloplication with annuloplasty ring and recovered uneventfully. Anticoagulation therapy was stopped at three months because of the increased risk of gastrointestinal bleeding in patients with PXE.

Conclusions: Careful attention should be paid to cases of PXE that could develop cardiovascular disease and the ensuing complications.

Keywords: Heart failure; mitral valve regurgitation; pseudoxanthoma elasticum (PXE); case report

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Introduction

Pseudoxanthoma elasticum (PXE) is a rare inherited systemic disease of connective tissue that primarily affects the skin, retina, and cardiovascular system due to mutations in the ATP-binding cassette subfamily C member 6 (*ABCC6*) gene (1). The most common cardiovascular involvement includes premature atherosclerosis, which leads to coronary artery disease in the absence of traditional risk factors (2-5). Moreover, histopathological analyses have revealed that the endocardium and valves are also affected among patients with PXE (6-8). Thus, the etiology of heart failure in this rare condition might be associated with a variety of situations, including coronary artery disease, valvular disease, and cardiomyopathy. However, the studies available to date did not explore the management or complications that may arise in patients with PXE and concomitant cardiovascular disease. Herein, we describe a case of PXE

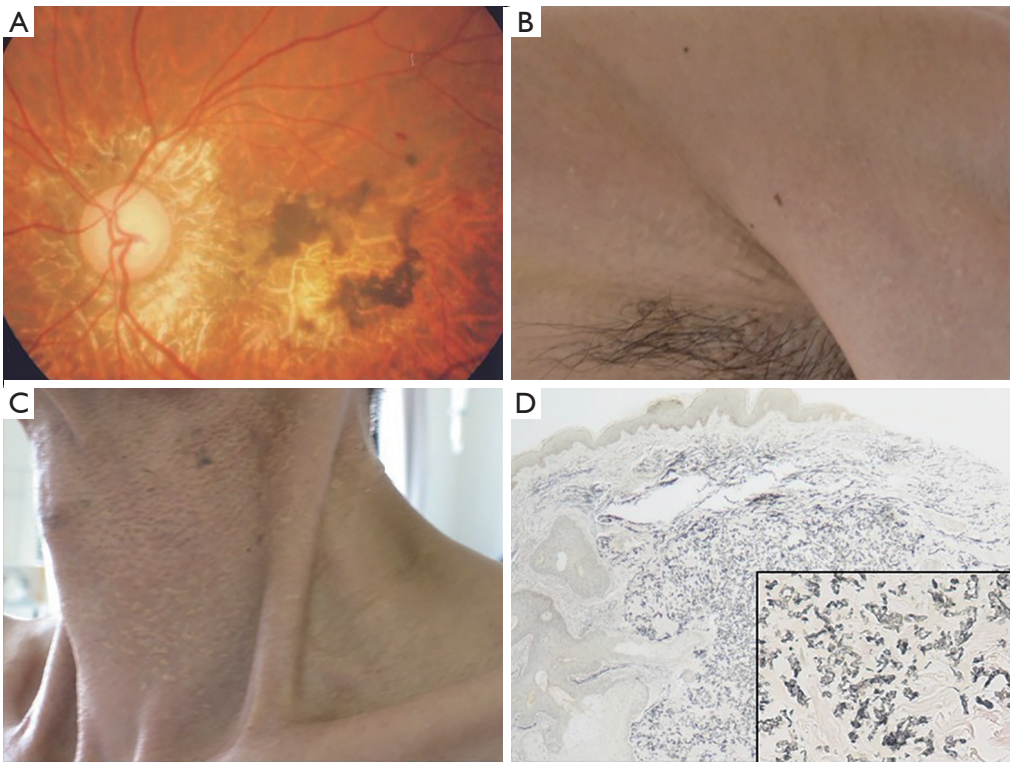

Figure 1 Non-cardiac examination of pseudoxanthoma elasticum. (A) Funduscopic examination shows the presence of angioid streaks in the left optic fundus. (B) Pebbly, yellowish lesions were observed within axillary folds. (C) Typical yellowish papules around the neck were detected upon careful examination. (D) Elastica van Gieson staining (original magnification ×40. Inset: same stain ×200) revealed characteristic fragmentation and clumping of elastic fibers in the middle and deep dermis.

presenting as heart failure in addition to severe mitral valve regurgitation that required surgical intervention. We present the following case in accordance with CARE reporting checklist (available at https://jxym.amegroups.com/article/view/10.21037/jxym-21-52/rc).

Case presentation

A 63-year-old male was admitted to our hospital with dyspnea. Prior to admission, he had been diagnosed clinically as having PXE at 56 years of age, based on the presence of angioid streaks in both eyes, as revealed by funduscopic examination when he experienced visual impairment (*Figure 1A*). Furthermore, he also exhibited yellow, pebbly skin lesions in the axillae (*Figure 1B*) and skin biopsy from his yellow papules around the neck (*Figure 1C*) revealed degeneration and fragmentation of the elastic fibers (*Figure 1D*). The patient had no history of rheumatic fever or infective endocarditis. Upon admission, chest X-ray showed pulmonary edema and bilateral pleural effusion. Transthoracic echocardiography in the parasternal long axis view showed enlarged left atrium and left ventricle with impaired left ventricular systolic function (*Figure 2A*,*2B*). Of note, the anterior mitral leaflet showed slight thickening and degenerative changes. Neither ruptured chords nor mitral annulus calcification were observed. Mitral valve regurgitation was observed towards the posterior left atrial wall (*Figure 2C*,*2D*). Coronary angiogram showed no significant stenosis. The grade of mitral valve regurgitation did not improve substantially after medical treatment with an angiotensin-converting inhibitor, beta-blocker, or diuretics, which indicated the need for surgical intervention. He underwent mitral annuloplication with annuloplasty ring and recovered uneventfully. Anticoagulation therapy was stopped after three months because of the increased risk of gastrointestinal bleeding in patients with PXE.

Whole exome sequencing was performed to determine the genetic cause of the PXE. We identified compound

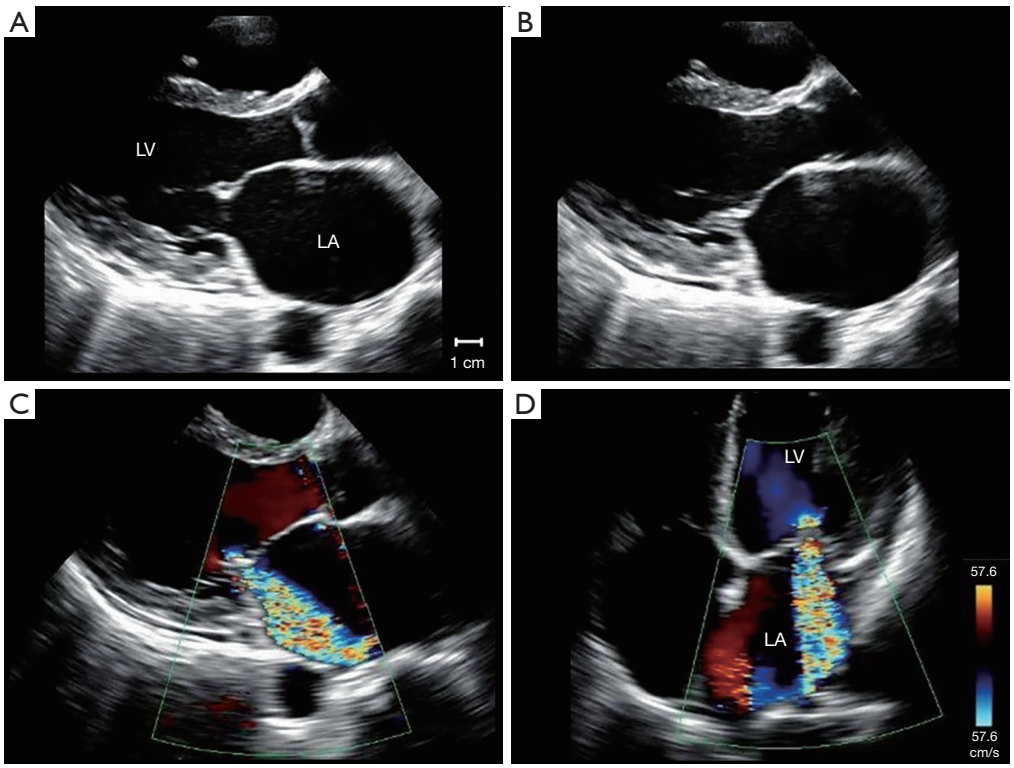

Figure 2 Findings of transthoracic echocardiography. (A,B) Transthoracic echocardiography in the parasternal long axis view in the end-diastolic and end-systolic phase. (C,D) Color Doppler image of severe mitral valve regurgitation in the parasternal long axis and 4-chamber view. LA, left atrium; LV, left ventricle.

heterozygous mutations in the *ABCC6* gene, one of which was a known mutation (c.2542delA or p.Met848CysfsTer83), while another was a novel mutation (c.1802T>C or p.Leu601Pro).

All procedures performed in this study were in accordance with ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

PXE is a hereditary, autosomal recessive, multisystemic disease affecting tissues rich in elastic fibers, such as the skin, retina, and cardiovascular system, due to mutations in the *ABCC6* gene (1). The prevalence of PXE is estimated to be between 1 in 50,000 and 1 in 70,000 (9). Cardiac complications associated with PXE focus on advanced coronary artery disease rather than valvular disease. Under these conditions, histopathological analysis in patients with PXE have also reported abnormal collagen or elastin of the endocardium and mitral valves leading to restrictive cardiomyopathy (6), mitral valve stenosis (7), and mitral valve prolapse (8). Although the histopathological examination of the skin biopsy specimen in the present case was fully compatible with PXE, the histopathological etiology via the endocardium and mitral valve could not be determined; thus, it remains unclear whether or not mitral valve regurgitation in the present case was caused by the essential malformation associated with PXE. However, the present case had no history of rheumatic fever nor infective endocarditis. Moreover, recent echocardiographic studies clearly demonstrated that mitral valve regurgitation was commonly observed in patients with PXE (10,11). Therefore, these results, in part, potentially suggest that severe mitral valve regurgitation in the present case might be considered as one of the morphological cardiovascular features in patients with PXE.

In the present case, dilated left ventricle was accompanied with severe mitral regurgitation. Chronic volume overload caused by severe mitral valve regurgitation might lead to left ventricular remodeling. To resolve this vicious cycle, mitral annuloplasty with artificial ring was performed with respect to left ventricular reverse remodeling and survival benefit. Although cardiovascular complications can be life-threatening and require surgical intervention, there is often a delay in seeking medical attention until serious complication occurs among patients with PXE (12,13). Moreover, these patients should also minimize risk of bleeding because gastro-intestinal hemorrhage can also be a serious complication among patients with PXE (14,15). Therefore, the need for a prosthetic valve appeared to be unsuitable for PXE due to a concern of long-term exposure under anticoagulation therapy.

Conclusions

Careful attention should be paid to cases of PXE that could develop cardiovascular disease and the ensuing complications.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://jxym.amegroups.com/article/view/10.21037/jxym-21-52/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jxym.amegroups.com/article/view/10.21037/jxym-21-52/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

References

1. Chassaing N, Martin L, Calvas P, et al. Pseudoxanthoma elasticum: a clinical, pathophysiological and genetic update including 11 novel ABCC6 mutations. J Med Genet 2005;42:881-92.
2. Bete JM, Banas JS Jr, Moran J, et al. Coronary artery disease in an 18 year old with pseudoxanthoma elasticum: successful surgical therapy. Am J Cardiol 1975;36:515-20.
3. Noji Y, Inazu A, Higashikata T, et al. Identification of two novel missense mutations (p.R1221C and p.R1357W) in the ABCC6 (MRP6) gene in a Japanese patient with pseudoxanthoma elasticum (PXE). Intern Med 2004;43:1171-6.
4. Miwa K, Higashikata T, Mabuchi H. Intravascular ultrasound findings of coronary wall morphology in a patient with pseudoxanthoma elasticum. Heart 2004;90:e61.
5. Anzai F, Kunii H, Kanno Y, et al. Successful revascularization of advanced coronary artery disease associated with pseudoxanthoma elasticum. J Cardiol Cases 2017;16:101-4.
6. Navarro-Lopez F, Llorian A, Ferrer-Roca O, et al. Restrictive cardiomyopathy in pseudoxanthoma elasticum. Chest 1980;78:113-5.
7. Fukuda K, Uno K, Fujii T, et al. Mitral stenosis in pseudoxanthoma elasticum. Chest 1992;101:1706-7.
8. Miki K, Yuri T, Takeda N, et al. An autopsy case of pseudoxanthoma elasticum: histochemical characteristics. Med Mol Morphol 2007;40:172-7.
9. Li Q, Jiang Q, Pfendner E, et al. Pseudoxanthoma elasticum: clinical phenotypes, molecular genetics and putative pathomechanisms. Exp Dermatol 2009;18:1-11.
10. Vanakker OM, Leroy BP, Coucke P, et al. Novel clinico-

molecular insights in pseudoxanthoma elasticum provide an efficient molecular screening method and a comprehensive diagnostic flowchart. Hum Mutat 2008;29:205.
11. Prunier F, Terrien G, Le Corre Y, et al. Pseudoxanthoma elasticum: cardiac findings in patients and Abcc6-deficient mouse model. PLoS One 2013;8:e68700.
12. Neldner KH. Pseudoxanthoma elasticum. Int J Dermatol 1988;27:98-100.
13. Araki Y, Yokoyama T, Sagawa N, et al. Pseudoxanthoma elasticum diagnosed 25 years after the onset of cardiovascular disease. Intern Med 2001;40:1117-20.
14. Sherer DW, Sapadin AN, Lebwohl MG. Pseudoxanthoma elasticum: an update. Dermatology 1999;199:3-7.
15. Goral V, Demir D, Tuzun Y, et al. Pseudoxantoma elasticum, as a repetitive upper gastrointestinal hemorrhage cause in a pregnant woman. World J Gastroenterol 2007;13:3897-9.

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