Pathohistological Evidence of Smoldering Inflammation in Rheumatic Heart Disease with Massive Left Atrial Calcification

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Abstract

A 74-year-old man, who had a history of a mitral valve replacement for rheumatic heart disease (RHD) 30 years previously, was admitted with progressive heart failure. Massive calcification was observed around the left atrium on multidetector CT, in addition to a late gadolinium enhancement (LGE)-positive layer adjacently outside of the calcification on MRI. He underwent a second mitral valve replacement for the prosthetic valve failure. Pathohistological analyses of a tissue section of the left atrial wall from a surgical specimen revealed lymphocyte and macrophage infiltration that coincided with the LGE-positive layer on MRI, suggesting the existence of sustained active inflammation even after the long period of RHD.

Key words: rheumatic heart disease, left atrial calcification, inflammation, pathohistology, cardiac MRI

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Introduction

Calcification of the left atrium (LA) is occasionally noted as an end result of rheumatic heart disease (RHD). It is considered to be the unfortunate product of inflammation (1), however, no studies have investigated its histology to explore the causes. We herein report for the first time a case of extensive LA calcification in a patient with RHD, which showed active inflammation with lymphocytes and macrophages that coincided with a late gadolinium enhancement (LGE)-positive area on MRI.

Case Report

A 74-year-old man was admitted to our hospital with progressive dyspnea. His medical record revealed a prior mitral valve replacement with bioprosthesis for rheumatic mitral stenosis 30 years previously and a stable course without systemic inflammatory evidence thereafter. On physical examination, his blood pressure was 144/66 mmHg and his pulse was 78 bpm and irregular. A blood test showed a high plasma brain natriuretic peptide level of 139 pg/mL. A nor-

mal serum C-reactive protein (CRP) level and white blood cell count suggested no systemic inflammation. Chest radiography revealed pulmonary congestion and bilateral pleural effusion compatible with congestive heart failure. Moderate mitral regurgitation due to the failed prosthetic valve was observed on Doppler echocardiography. Right-sided heart catheterization revealed pulmonary hypertension with a mean pressure gradient of 47 mmHg due to a moderate degree of mitral regurgitation caused by the prosthetic valve failure (Fig. 1A). Fluoroscopic radiography showed a round-shaped radiopaque structure at the LA (Fig. 1B), which was not apparent 30 years prior, and multidetector CT demonstrated massive calcification around the LA (Fig. 1C, D). Cardiac MRI showed an enlarged LA with a thickened area of an irregular low density in the wall, suggestive of massive endocardial calcification in the LA (Fig. 2A). There was a layer of positive LGE located adjacently outside of the calcification (Fig. 2B). This layer also showed a high signal intensity on the T2-weighted MRI image, suggestive of edematous tissue caused by inflammation (Fig. 2C). The patient required a second mitral valve replacement for the bioprosthetic valve failure.

Tissue sections of the LA wall from a surgical specimen

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Figure 1. A: Doppler echocardiography showing mitral regurgitation (MR) through the mitral artificial valve, causing increased left atrial pressure. B: A fluoroscopic X-ray at the left ventricular pressure measurement shows round-shaped calcification in the position of the left atrium. C: Multi-detector CT demonstrated massive calcification around the left atrium. D: 3D construction from multidetector CT shows a characteristic round-shaped appearance. LA: left atrium, LV: left ventricle, RA: right atrium, RV: right ventricle, Ao: aorta

Figure 2. A: Cardiac MRI shows an enlarged LA with a thickened area of irregular low density in the wall (arrowheads), suggestive of abnormal calcification constituting a large portion of the endocardium. B: A cardiac MRI image 10 minutes after the injection of gadolinium. Arrows indicate a late gadolinium enhancement (LGE)-positive layer adjacently outside of the calcified layer around the left atrium. C: A high-signal intensity on a T2-weighted MRI image around the left atrium was observed, indicating an edematous lesion due to inflammation (arrows). LA: left atrium, LV: left ventricle, RA: right atrium

Figure 3. A: A low-power field image of Hematoxylin and Eosin staining of the resected left atrial specimen. Massive calcification was observed in the endocardium of the left atrium. B: A high-power field image of the square frame in Fig. 3A. Lymphocytes (arrowheads) were scattered in the outer layer of calcification. C: Immunohistochemical staining with CD68 shows macrophages infiltration in the left atrial wall. D: Immunohistochemical staining shows positive reactivity for tenascin-C in the interstitium of the left atrial wall (arrowheads). This finding indicates ongoing matrix remodeling by inflammatory cells at the infiltrating site. LA: left atrium

were stained with hematoxylin and eosin, showing marked calcification in the endocardium of the LA (Fig. 3A). Infiltrating lymphocytes were diffusely scattered in the layer of the LA wall outside the calcification (Fig. 3B). Immunohistochemistry (IHC) with CD68 (#M0814, 1:1000; Dako, Tokyo, Japan) revealed macrophages also existed in this area (Fig. 3C). In addition, IHC with tenascin-C antibody (#10337, 1:1000; Immuno-Biological Laboratories, Fujioka, Japan), which is one of the markers of extracellular matrix (ECM) remodeling and the inflammatory response, was diffusely positive in the intercellular space (Fig. 3D). An inflammatory lesion observed in the LA wall appeared to coincide with the LGE-positive and T2 high-signal intensity layer on cardiac MRI.

Discussion

Extensive calcification in the LA wall, described as the “coconut atrium” or “porcelain atrium,” is an infrequent complication in patients with RHD. Calcification reportedly prevents the enlargement of the LA, resulting in reduced compliance (2). The decreased reservoir function of the LA

can lead to a decreased cardiac output despite a fair left ventricular function. In addition, the increased LA pressure due to non-severe mitral regurgitation may eventually cause the onset of both pulmonary arterial hypertension and right heart pressure-overload, thus leading to tricuspid valve dysfunction.

The etiology of LA calcification in RHD is considered to be recurrent and extensive episodes of rheumatic inflammation of the LA (3). Hematoma and inflammation after mitral valve replacement, chronic wall burden with mitral valve disease and adhesion of blood due to atrial fibrillation have been proposed as additional influencing factors on atrial calcification. Severe calcification, such as that observed in this case, is considered to be the unfortunate end product of inflammation, however, no histological study has been previously performed. We demonstrated that inflammatory cells, including lymphocytes and macrophages, infiltrated the LA wall with severe calcification, indicating that ongoing inflammatory response and tissue remodeling may occur despite extensive calcification. We speculate from this finding that long-term persistent LA inflammation caused by a rheumatic fever may lead to the development of necrosis of the

regional tissue with inflammation, cause hyperextension of the LA wall, and ultimately result in calcification in patients with RHD.

Persistent inflammation in rheumatic patients was previously reported along with sustained elevation of the CRP level and a pathology featuring persistent inflammation in forms such as chronic inflammatory cell infiltration in RHD (4, 5). Long-lasting inflammation might be a cause of calcification, as active inflammation is a potential concern with cardiac valve calcification in patients undergoing continuous ambulatory peritoneal dialysis (6). In addition, this speculation is supported by the presence of a tenascin-C positive area associated with infiltratory inflammatory cells in this case. Tenascin-C does not appear in the normal adult heart, but is observed at the periphery of necrotic or degenerating cardiomyocytes in foci of inflammation, the expression level correlating with histological evidence of inflammatory activity (7). Positive tenascin-C expression observed concurrently with infiltrating inflammatory cells suggests activation of the monocyte-macrophage system and consequent ECM remodeling. Furthermore, positive LGE and T2 high-intensity MRI images imply smoldering active inflammation with severe calcification in LA, as those MRI findings indicate cellular edema or inflammation (8-10).

Our findings of persistent inflammatory cell infiltration into the LA in RHD suggest that anti-inflammatory therapy might be effective in preventing the progression of calcification even in the chronic phase. The class I recommendation in the current guideline is the administration of antibiotics as secondary prevention for 10 years or until the age of 40 years for patients who develop RHD (11). The long-term therapy for inflammatory cell infiltration might have prevented the development of calcification in this case.

The authors state that they have no Conflict of Interest (COI).

References

1. Harthorne JW, Seltzer RA, Austen WG. Left atrial calcification. Review of literature and proposed management. *Circulation* **34**: 198-210, 1966.
2. Murray JA, Kennedy JW, Figley MM. Quantitative angiocardiology. II. The normal left atrial volume in man. *Circulation* **37**: 800-804, 1968.
3. Gedgaudas E, Kieffer SA, Erickson C. Left atrial calcification. *Am J Roentgenol Radium Ther Nucl Med* **102**: 293-296, 1968.
4. Gölbası Z, Uçar O, Keles T, et al. Increased levels of high sensitive C-reactive protein in patients with chronic rheumatic valve disease: evidence of ongoing inflammation. *Eur J Heart Fail* **4**: 593-595, 2002.
5. Chopra P, Bhatia ML. Chronic rheumatic heart disease in India: a reappraisal of pathologic changes. *J Heart Valve Dis* **1**: 92-101, 1992.
6. Wang AY, Woo J, Wang M, et al. Association of inflammation and malnutrition with cardiac valve calcification in continuous ambulatory peritoneal dialysis patients. *J Am Soc Nephrol* **12**: 1927-1936, 2001.
7. Imanaka-Yoshida K, Hiroe M, Yasutomi Y, et al. Tenascin-C is a useful marker for disease activity in myocarditis. *J Pathol* **197**: 388-394, 2002.
8. Giri S, Chung YC, Merchant A, et al. T2 quantification for improved detection of myocardial edema. *J Cardiovasc Magn Reson* **11**: 56, 2009.
9. Gutberlet M, Spors B, Thoma T, et al. Suspected chronic myocarditis at cardiac MR: diagnostic accuracy and association with immunohistologically detected inflammation and viral persistence. *Radiology* **246**: 401-409, 2008.
10. Abdel-Aty H, Boyé P, Zagrosek A, et al. Diagnostic performance of cardiovascular magnetic resonance in patients with suspected acute myocarditis: comparison of different approaches. *J Am Coll Cardiol* **45**: 1815-1822, 2005.
11. Gerber MA, Baltimore RS, Eaton CB, et al. Prevention of rheumatic fever and diagnosis and treatment of acute *Streptococcal pharyngitis*: a scientific statement from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young, the Interdisciplinary Council on Functional Genomics and Translational Biology, and the Interdisciplinary Council on Quality of Care and Outcomes Research: endorsed by the American Academy of Pediatrics. *Circulation* **119**: 1541-1551, 2009.