Time-Dependent Changes in Porcelain Aorta and Aortic Stenosis in a Patient with Systemic Lupus Erythematosus

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Summary
Porcelain aorta, defined as extensive calcification of the ascending aorta or aortic arch, is reported as a risk factor for embolic stroke during cardiac surgery. However, the time course of progression of aortic calcification leading to porcelain aorta has not been elucidated. We herein describe a 70-year-old woman who was followed up for systemic lupus erythematosus and antiphospholipid syndrome for approximately 20 years. A routine computed tomography scan revealed progression of ascending aortic calcification to porcelain aorta. The calcification was absent during the preceding 12 years, partial 6 years later, and total after another 3 years. Computed tomography also demonstrated aortic and mitral valve calcification in the development of porcelain aorta. During the 3 years prior to the last admission, annual echocardiography examinations showed progression of calcific aortic stenosis with symptoms. The patient was admitted to our institution for aortic valve replacement. Considering the high risk of perioperative stroke associated with porcelain aorta, transcatheter aortic valve implantation was performed. Postoperative transthoracic echocardiography revealed improvement of the aortic stenosis with no symptoms. The present case revealed aortic calcific progression to porcelain aorta during an approximately 10-year period with deterioration of aortic stenosis within a short time. The aortic and valvular calcification could be attributed to the inflammatory process of systemic lupus erythematosus and antiphospholipid syndrome. The presence of aortic and mitral annular calcification in the serial imaging can provide information on aortic and valvular atherosclerotic progression, which may be modifiable by early steroid-lowering therapy.

Key words: Aortic calcification, Time course, Computed tomography, Transcatheter aortic valve implantation, Connective tissue disease, Long-term steroid therapy

Porcelain aorta (PA), defined as extensive calcification of the ascending aorta or aortic arch, is reported as a risk factor for cardiovascular disease. Although the prevalence of PA is low in the general population, it is approximately 7.5% among patients with aortic stenosis (AS). An important clinical implication of PA is an increased risk of embolic stroke during cardiac surgery. However, the time course of progression of aortic calcification leading to PA has not been elucidated. We herein describe the time-dependent changes of PA and AS in a patient with systemic lupus erythematosus (SLE).

Case Report
A 70-year-old woman with a history of hypertension, SLE, and antiphospholipid syndrome (APS) was admitted to our institution for severe AS. She had been diagnosed with SLE and APS in the preceding 19 years and treated with steroids and immunosuppressive agents. Twelve years before the last admission, the patient had a cumulative glucocorticoid dose of approximately 20 g and was evaluated for interstitial pneumonia because of the development of Sjögren’s syndrome. Screening transthoracic echocardiography and computed tomography (CT) demonstrated a tricuspid sclerotic aortic valve without stenosis and subtle aortic calcification (Figure A). Carotid ultrasound revealed bilateral carotid artery plaques. Positron emission tomography–CT (PET-CT) revealed no abnormal uptake in the aortic wall, providing no evidence for aortitis. Thereafter, routinely performed CT scans to check for interstitial pneumonia showed progression of ascending aortic calcification; the calcification was absent in the preceding 12 years, partial 6 years later (Figure B), and total after another 3 years (Figure C). During the 3 years prior to the last admission, aortic valve stenosis with calcification had also progressed as shown by annual echocardiography examinations [maximum velocity (Vmax) of 2.98 m/second and mean pressure gradient (PG) of 19.0 mmHg before 3 years; Vmax of 3.60 m/second and mean PG of 31.0 mmHg before 2 years; and Vmax of 3.80 m/second and...
mean PG of 34.0 mmHg in the previous year]. The patient also experienced exertional dyspnea and syncope and was admitted for aortic valve replacement.

On admission, the patient had received a cumulative prednisone dose of 60 g. Her blood pressure was 104/60 mmHg and heart rate was 63 beats/minute with a regular rhythm. A systolic ejection murmur was heard at the right second intercostal space. Laboratory evaluation showed controlled SLE with almost normal antinuclear antibodies, complement, double- and single-stranded DNA antibodies, C-reactive protein, and erythrocyte sedimentation rate. The blood examination showed mild renal impairment and a mildly elevated brain natriuretic peptide level. The serum concentrations of calcium, phosphate, and intact parathyroid hormone, all of which are markers of calcium and phosphate metabolism, were within the reference ranges. No ST segment abnormality was found on electrocardiography, but bilateral lower lung reticulation was found on chest X-rays. Transthoracic echocardiography revealed further progression of AS (Vmax of 4.09 m/second, mean
Table. Previous Reports on Porcelain Aorta and Severe Aortic Stenosis with Connective Tissue Disease and the Present Case

| Age (years) | Sex | Valvular disease | CTD | CTD duration (y) | Procedure | Complications |
|------------|-----|-----------------|-----|-----------------|-----------|---------------|
| 65         | F   | Severe AS       | RA  | NA              | SAVR      | -             |
| 65         | F   | Severe PVL after AVR (45 y, AS), mild MR, mild TR | TA  | > 20            | Bentall operation + MVP, TAP | - |
| 43         | M   | Severe AS after Bentall operation | Behget | 7 | PCI → TAVI (valve-in-valve) | - |
| 73         | F   | Severe AS, mild MR | SLE | NA | OPCABG + TAVI (transaortic) | - |

Present case: 70 F Severe AS, mild MS SLE, APS 19 TAVI -

APS indicates antiphospholipid syndrome; AS, aortic stenosis; AR, aortic regurgitation; AVR, aortic valve replacement; CTD, connective tissue disease; F, female; M, male; MR, mitral regurgitation; MVP, mitral valvuloplasty; MVR, mitral valve replacement; MS, mitral stenosis; NA, not available; OPCABG, off-pump coronary artery bypass grafting; PCI, percutaneous coronary intervention; PVL, paravalvular leakage; RA, rheumatoid arthritis; SAVR, surgical aortic valve replacement; SLE, systemic lupus erythematosus; TA, Takayasu aortitis; TAP, tricuspid annuloplasty; TAVI, transcatheter aortic valve implantation; and TR, tricuspid regurgitation.

PG of 41.0 mmHg, and aortic valve area of 0.80 cm²) and mild mitral stenosis with mitral annular calcification (MAC); left ventricular systolic function was normal. CT also showed diffuse, generalized calcification of the ascending aorta extending to the descending aorta, suggesting PA (Figure D).

Although the Society of Thoracic Surgeons mortality risk was 5.8%, surgical aortic valve replacement was not feasible because of the high risk of stroke with PA. Therefore, transcatheter aortic valve implantation (TAVI) was performed. A 26-mm balloon-expandable Sapien 3 valve (Edwards Lifesciences, Irvine, CA, USA) was successfully implanted under rapid ventricular pacing. Postoperative transthoracic echocardiography revealed improvement in the AS (Vmax of 4.09 to 1.60 m/second, mean PG of 41.0 to 5.2 mmHg, and aortic valve area of 0.80 to 3.15 cm²) with trivial paravalvular leakage. The patient remained asymptomatic and required no further intervention.

Discussion

In the present case, aortic calcification progressed to PA during an approximately 10-year period with deterioration of AS in the short term. The patient’s condition was finally treated with TAVI. PA is defined as completely or near completely circumferential calcification of the ascending aorta or aortic arch.13 The underlying mechanism has been considered to involve intimal atherosclerotic calcification associated with lifestyle diseases such as hypertension and diabetes mellitus, and medial calcification correlated with a nonatherosclerotic process.13 In the intimal atherosclerotic calcification process, extracellular matrix vesicles, generated from intimal proliferation and apoptosis of macrophage foam cells and vascular smooth muscle cells (VSMCs) following endothelial injury, become calcified because of bone-associated calcium-regulatory proteins produced by these cells, elastin acting as a calcifying protein, and plaque inflammation elevating the extracellular ion concentration.10 Medial calcification, another mechanism of PA, is associated with uremia, radiation, or vasculitis, transforming medial VSMCs into osteoblasts that produce various bone-associated proteins; downregulating matrix G1a protein, which inhibits medial calcification; and causing VSMC apoptosis and elastin degradation.13 In patients with SLE, various immunological processes are associated with acceleration of aortic sclerosis,14 suggesting the progression of PA with intimal calcification. In the present case, sequential CT and echocardiographic imaging revealed aortic valvular calcification (AVC) and MAC, reflecting atherosclerosis.15 Particularly in SLE, MAC reportedly has a strong correlation with atherosclerotic change.16 Another study also showed a higher prevalence of progression of aortic calcification for 4 years in patients with SLE than in normal subjects.17 Our patient had little evidence of medial calcification because she had no history of uremia or radiation and no evidence of aortitis (i.e., no abnormal uptake on PET-CT or elevation of inflammatory markers). Based on the presence of aortic and mitral valvular calcification and bilateral carotid artery plaques, which reflect atherosclerosis, intimal calcification was considered to be the mechanism of PA.

Our patient also showed sequential progression from mild to severe AS for 3 years before admission. A previous cohort study showed an association between SLE and valvular heart disease (AS, aortic regurgitation, mitral stenosis, and mitral regurgitation) and a higher prevalence of valvular heart disease with antiphospholipid antibodies.7 In a 4-year observational study of patients with SLE,18 11% of the patients had Libman-Sacks endocarditis (LSE), 34% of patients with LSE had aortic valvar disease, and half of patients with aortic valvar disease exhibited mild to moderate or severe progression. The mechanism of valvular disease was considered to be fibrosis, degeneration, and dysfunction due to involvement and organization associated with fibrin and thrombosis, which was accelerated by antiphospholipid antibodies.7 Another report demonstrated that the higher prevalence of AVC and MAC in young patients with SLE was associated with not only conventional atherosclerotic factors but also antiphospholipid antibodies, leading to valvular heart disease.9 In our patient, the lack of LSE and the presence of AVC, MAC, and PA in serial echocardiographic and CT imaging suggested atherosclerotic progression of AS. Several reports have described cases of severe AS with PA in patients with connective tissue disease (Table). These cases suggest the association of aortic calcification with
female sex and a relatively long duration of connective tissue disease. Among these cases, no conventional atherosclerotic risk factors were evident, indicating a correlation between aortic calcification and connective tissue disease. No complication occurred during the procedure, possibly because TAVI is a less invasive procedure. The time course of AS and PA was not described in previous cases. This case is significant in revealing the time course of AS and progression of aortic calcification to PA in a patient with SLE. In addition, higher corticosteroid dose was an independent risk for aortic calcific progression as well as increased lupus disease activity. It may be partly explained by the effect of glucocorticoids on the osteogenic differentiation of pericytes and the downregulation of genes inhibiting mineralization. A previous cross-sectional study also demonstrated the link between prednisone use and AVC. These analyses suggested that long-term use of steroids could accelerate aortic and aortic valvular calcification in this case. In fact, the patient had received a cumulative prednisone dose of ≥ 60 g, which is comparable with the findings in the Outcome of Rheumatoid Arthritis Longitudinal Evaluation cohort; namely, a summed glucocorticoid dose of ≥ 20 g was an independent risk factor for cardiovascular events including acute coronary syndrome in individuals with rheumatoid arthritis. Given the controlled lupus disease activity, early reduction in glucocorticoids or switch to other immunosuppressive drugs, which might modify the calcific process, should be considered. Further investigations are warranted to elucidate the effects of early steroid-lowering strategy on aortic and valvular calcification.

**Conclusion**

The present case demonstrated progression of aortic calcification to PA over a 10-year period and deterioration of AS for several years. The acceleration of atherosclerotic calcification was possibly associated with the presence of SLE, APS, and long-term steroid therapy. AVC and MAC could be a marker of progression of valvular and aortic atherosclerosis, and if inflammatory disease is controlled, early steroid reduction may result in modifying the development of PA and AS.

**Disclosure**

**Conflicts of interest:** The authors have no conflicts of interest to declare.

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