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EDITORIAL COMMENT

The Thickened Valve*

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In this issue of *JACC: Case Reports*, Bell et al. (1) present an interesting case report describing right- and left-sided valvular heart disease in a 73-year-old woman being treated with a selective serotonin reuptake inhibitor (SSRI) (citalopram) for major depressive episodes with psychosis. Intriguingly, the past medical history was notable for a carcinoid tumor with mesenteric metastases. The tumor was surgically resected, and the patient was treated with monthly octreotide injections for 8 years until the patient was considered to be in remission based on laboratory and imaging studies. The patient subsequently developed characteristic triad symptoms of carcinoid syndrome 3 years later including flushing, diarrhea, and worsening dyspnea on exertion with elevated N-terminal pro-B-type natriuretic peptide, chromogranin A and urine 5-hydroxyindoleacetic acid. The echocardiographic imaging during the current admission revealed severe right- and left-sided valvular regurgitation with thickened leaflets, which were not seen in prior echocardiograms 3 years ago. There was no evidence of recurrence of tumor both on octreotide scan and computed tomography angiograms of the chest and abdomen. The clinical picture was considered consistent with carcinoid syndrome-like valvular heart disease in the setting of SSRI use. In particular, the involvement of the left-sided valve supports drug-induced valvular heart disease.

The valve thickening other than calcification could result from myxomatous degeneration, post-inflammatory valvular involvement (e.g., rheumatic heart disease, endocarditis, and autoimmune diseases such as lupus), and less frequently carcinoid heart valve disease. The rare causes of valvular heart disease include storage diseases and drug-related valvular pathology such as seen in the present case with SSRI use; other drugs include ergotamine and anorectic agents (2,3). Distinct pathologic alterations seen in valves in carcinoid heart disease, rheumatic heart disease, and myxomatous degeneration are discussed subsequently (**Figures 1 to 3**).

In carcinoid heart disease, the endocardium of the right-sided chambers of the heart, tricuspid and pulmonary valves, the subvalvular apparatus (chordae tendineae and papillary muscles), venae cavae, pulmonary artery, and coronary sinus are involved (4). The right-sided valves account for 92% of the surgically excised valves (5). Clinically, tricuspid valve is affected in 90% of patients with established carcinoid heart disease (6). The valvular dysfunction in carcinoid heart disease occurs due to the formation of fibrous plaques that lead to thickening of the leaflets and encase the subvalvular apparatus; the fibrotic involvement may result in varying degrees of valve stenosis and regurgitation. These plaques are composed of myofibroblasts and extracellular matrix with neovascularization and mild chronic inflammation; extracellular matrix comprises of collagen and myxoid ground substance. It is important to recognize that these plaques are deposited on the valvular surfaces and do not destroy the underlying valve morphology. In the right heart, these surface plaques could lead to the adherence of the tricuspid valve to the mural endocardium and valve regurgitation. On echocardiography, diffuse thickening, loss of valve curvature, and significant impairment of mobility of the tricuspid valve leaflets are seen. The thickening

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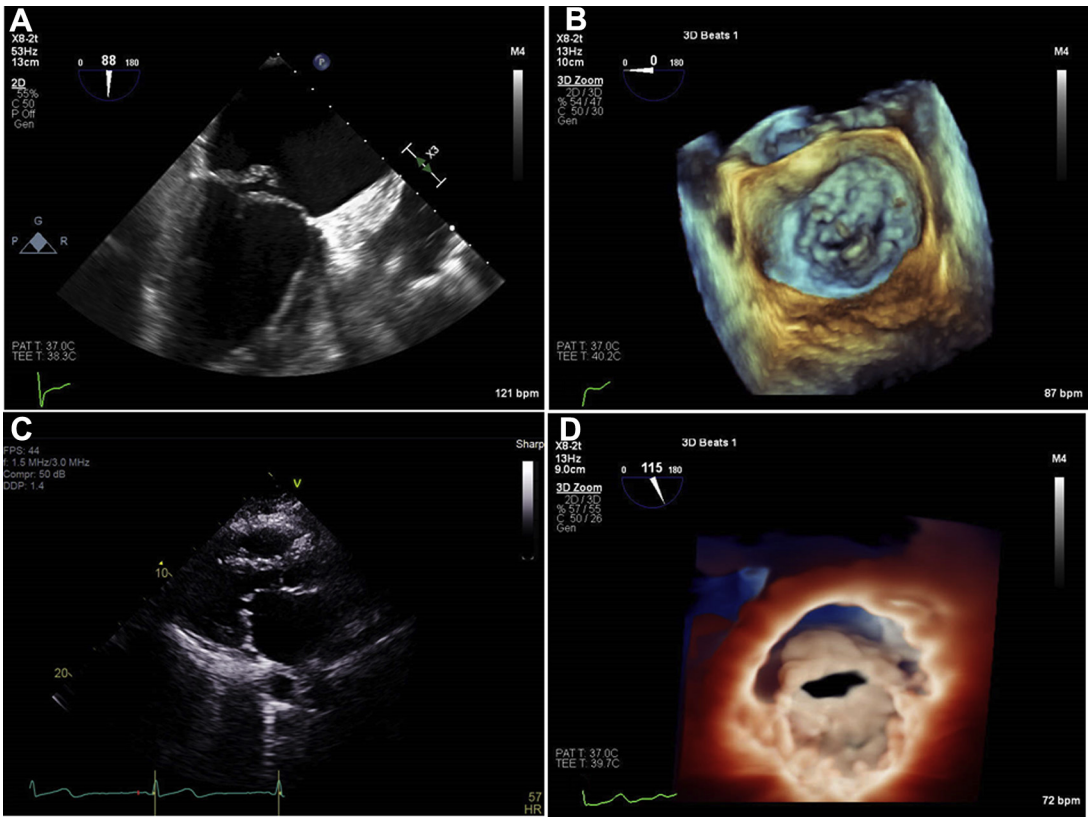
FIGURE 1 Transesophageal Echocardiography of a Barlow Mitral Valve and Rheumatic Mitral Stenosis

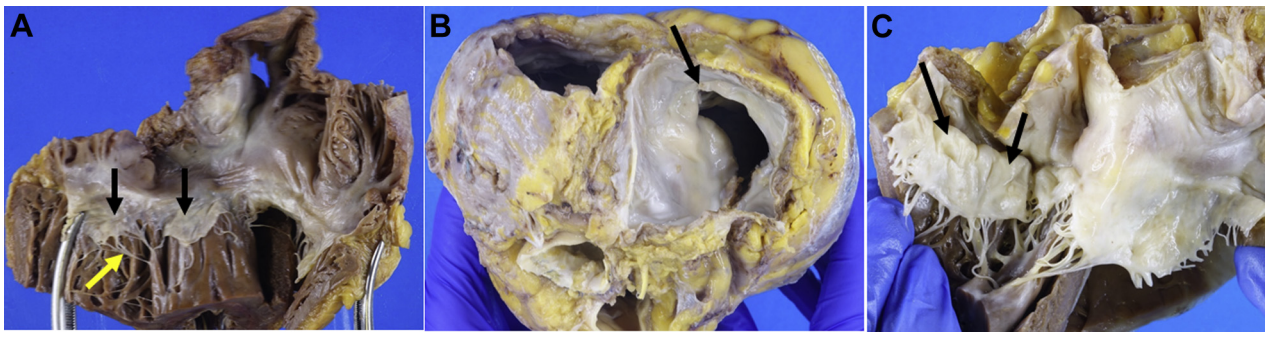


(A) Two-dimensional transesophageal echocardiography (TEE) of a thickened Barlow valve with a flail segment. **(B)** The same valve on 3-dimensional TEE, atrial perspective showing multiscallop prolapse with flail P2 scallop. **(C)** Two-dimensional transthoracic echocardiography with rheumatic mitral stenosis. **(D)** Three-dimensional TEE of mitral stenosis, ventricular perspective, transillumination rendering showing commissural fusion and restricted valve opening.

typically extends to the subvalvular apparatus, which contributes to the retraction of the tricuspid valve leaflets. In advanced cases, thickened, retracted, echo bright tricuspid leaflets appear fixed in a "semi-open" position resulting in some degree of tricuspid stenosis as well as severe regurgitation with a characteristic triangular spectral Doppler pattern. The pulmonic valve typically shows a similar echocardiographic pattern of leaflet thickening, impaired mobility, and poor coaptation resulting in a combination of valvular stenosis and regurgitation. Left-sided involvement is seen in <10% of cases, especially in patients with liver metastases or pulmonary carcinoid, or in those with patent foramen ovale (7). There is no evidence of commissural fusion as seen in post-inflammatory valvular diseases and hooding of the leaflets as seen in floppy valves. Other accompanying manifestations of carcinoid heart disease include coronary artery vasospasm (8), ventricular tachycardia (9), and metastatic carcinoid spread to the myocardium (5).

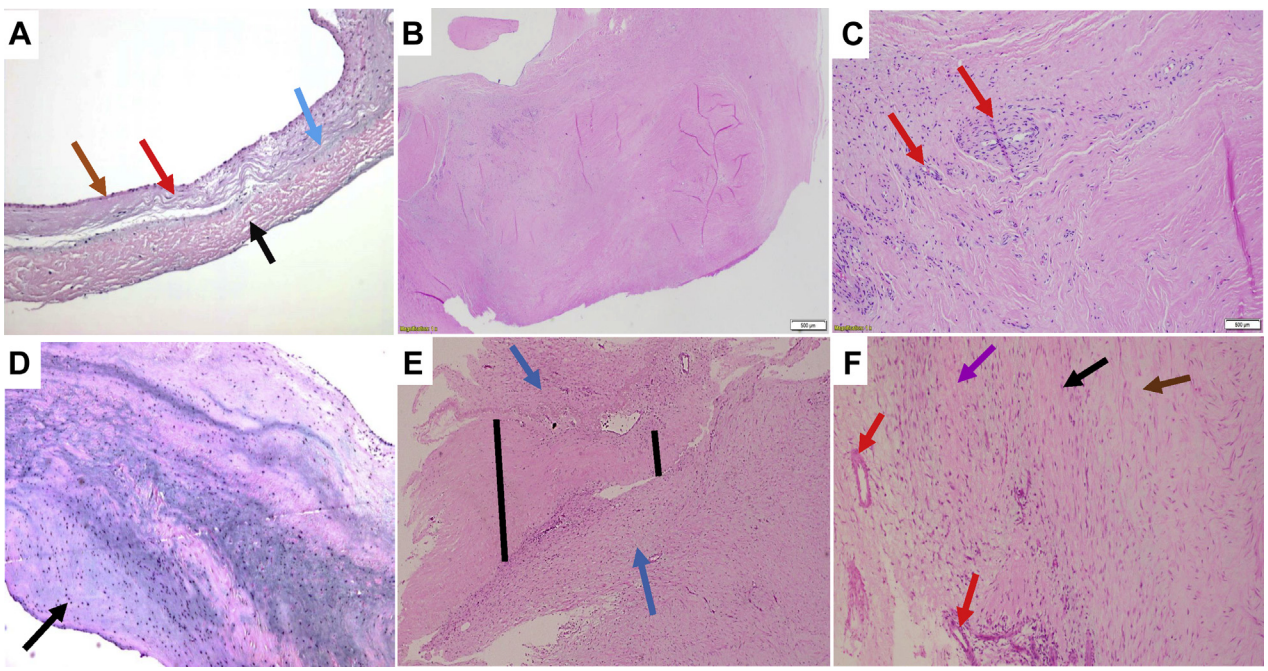
The mitral valve is the most commonly affected valve in rheumatic heart disease, followed by the aortic, tricuspid, and pulmonary valves. The valves are fibrotic and demonstrate commissural fusion. The valves are often calcified, and the chordae tendineae thickened and shortened. Histologically, the valves in rheumatic heart disease show fibrosis, neovascularization, and chronic inflammation. However, in contrast to the valvular morphology in carcinoid heart disease, wherein the valvular structure is intact and the fibrous plaques are layered on the endocardial surfaces of the valve, the underlying valve architecture is destroyed in valves afflicted by rheumatic heart disease (10). On echocardiography,

FIGURE 2 **Gross Images of 3 Explanted Hearts**



(A) Normal mitral valve. The cusps are thin and translucent **(black arrows)** and the chordae tendinae **(yellow arrow)** are thin and delicate. **(B)** Mitral valve of the heart shows thickened leaflets with commissural fusion **(black arrow)**. The orifice of the mitral valve viewed from the left atrial aspect has a fish mouth appearance due to the fused commissure. **(C)** The mitral valve has myxomatous degeneration. Hooding of the posterior cusp **(black arrows)** is present.

FIGURE 3 **Histologic Features of Normal, Rheumatic, Myxomatous, and Carcinoid Mitral Valve**



(A) The normal valve is lined by endothelial cells **(brown arrow)** and is composed of 3 distinct layers: fibrosa, ventricularis, and spongiosa. The fibrosa **(black arrow)** provides structural support and is composed of compact collagen fibers; the spongiosa **(blue arrow)** is composed of extracellular matrix, elastic fibers, and valvular interstitial cells; the ventricularis **(red arrow)** contains large amounts of elastic fibers. **(B, C)** histological images of post-inflammatory valvular disease, the most common cause of which is rheumatic heart disease. The valves are thickened due to fibrosis, and there is disruption of the normal layers of the valve, as seen at low-power magnification in **B**. On higher magnification, neovascularization **(red arrows)** is present. **(D)** In myxomatous degeneration, thickening of the leaflets is due to accumulation of glycosaminoglycans in the spongiosa layer **(black arrow)**, with attenuation of the fibrosa layer. **(E, F)** Valvular involvement in carcinoid heart disease. **(E)** Fibrous plaques **(blue arrows)** are layered on the valve leaflet **(black lines)**. **(F)** At higher magnification, the fibrous plaques are composed of collagen **(purple arrow)**, myofibroblasts **(black arrow)**, ground substance **(brown arrow)**, and neovessels **(red arrow)**.

commissural fusion is the most characteristic feature of the rheumatic valve disease. In mitral stenosis, it manifests as characteristic doming of the anterior mitral leaflet in diastole along with restricted mobility of the posterior mitral leaflet. Commissural fusion results in a funnel-like narrowing of the mitral valve with a typical "fish mouth" appearance. In addition, valve thickening, valve and commissural calcification, and subvalvular involvement are seen, all of which are important components for the assessment of percutaneous intervention feasibility.

Myxomatous degeneration can be sporadic or seen in patients with Marfan syndrome, Ehlers-Danlos syndrome, or osteogenesis imperfecta. The valves are thickened, gelatinous, and have elongated and thinned chordae. The thickening of the leaflets is due to accumulation of glycosaminoglycans in the spongiosa layer with attenuation of the fibrosa. The posterior leaflet is most commonly involved. Barlow's disease is the term used when the entire valve is involved. There is no evidence of commissural fusion, and calcification is usually not seen (11,12). On echocardiography, myxomatous Barlow disease appears as thickening and redundancy of the mitral valve leaflets, which can be associated with valve prolapse, flail segments, and mitral annular disjunction. The tricuspid valve can be similarly affected in some patients. On the other hand, fibroelastic deficiency results in a localized prolapse or flail valve segment without diffuse valve thickening.

In conclusion, although rare, carcinoid heart disease results in a unique pattern of cardiac pathology and valvular dysfunction, distinct from other more common causes of valvular involvement. Understanding the pathologic basis of this condition helps highlight the features commonly seen on in vivo cardiac imaging.

AUTHOR RELATIONSHIP WITH INDUSTRY

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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