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CASE REPORT

ADVANCED

CLINICAL CASE

Mucopolysaccharidosis Type I Diagnosed by Aortic and Mitral Valve Replacement

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ABSTRACT

A 32-year-old developmentally delayed man presenting with dyspnea was found to have severe aortic and mitral valve stenosis. After double valve replacement, unique histologic findings prompted a genetics evaluation, ultimately leading to the diagnosis of mucopolysaccharidosis type I, a rare lysosomal storage disorder with high rates of cardiac manifestations. (**Level of Difficulty: Advanced.**) (J Am Coll Cardiol Case Rep 2021;3:1891–1894) © 2021 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

A 32-year-old man with developmental delay presented to his primary care physician with progressively worsening exertional dyspnea. His caretaker described severe shortness of breath, requiring the patient to rest after climbing a few stairs. The results of physical examination were notable for coarse facial features, a prominent forehead and brow ridge, and a shortened neck. He had limited range of motion throughout his upper and lower extremities, with a stiff and wide-based gait. Cardiac auscultation revealed a grade III/VI systolic murmur over the right upper sternal border and grade II/VI diastolic murmur over the apex, without evidence of decompensated heart failure. A transthoracic echocardiogram (TTE) demonstrated moderate to severe mitral and aortic stenosis, prompting a referral to cardiology.

LEARNING OBJECTIVES

- To understand the clinical presentation of mucopolysaccharidosis
- To demonstrate the high rates of cardiovascular complications in patients with mucopolysaccharidosis
- To maintain a broad differential for valvular pathology, particularly in individuals presenting with unexplained syndromic features

MEDICAL HISTORY

The patient had a history of developmental delay with a gradual loss of milestones and abilities since he was 17 years old. One year before presentation he began experiencing progressive loss of peripheral vision; ophthalmologic evaluation revealed retinal degeneration and bilateral optic disc edema. Magnetic resonance imaging of the brain showed ventriculomegaly, which was concerning for hydrocephalus and global parenchymal volume loss.

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ABBREVIATIONS AND ACRONYMS

CNS = central nervous system

GAG = glycosaminoglycan

LVOT = left ventricular outflow tract

MPS = mucopolysaccharidosis

TTE = transthoracic echocardiogram

DIFFERENTIAL DIAGNOSIS

Important diagnostic considerations in this young adult included rheumatic heart disease, congenital malformation (e.g., bicuspid valve), and syndrome-associated valvular disease (e.g., Marfan syndrome, Jacobsen syndrome, and mucopolysaccharidoses).

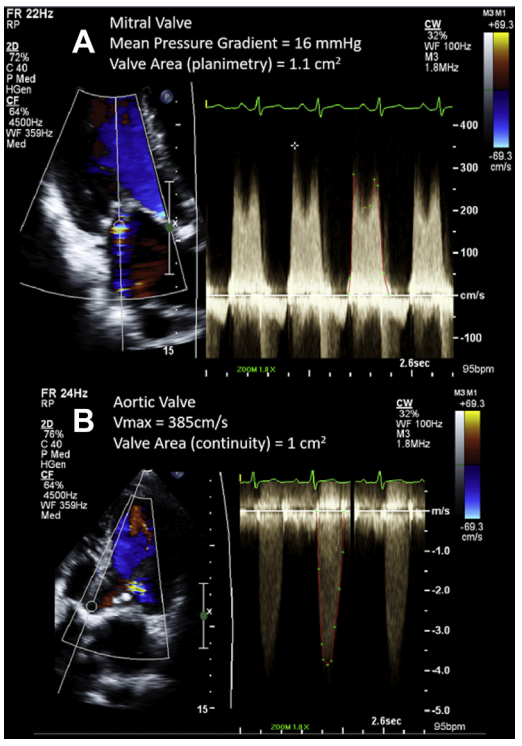
INVESTIGATIONS

An electrocardiogram showed sinus tachycardia with a heart rate of 114 beats/min, 1 premature ventricular beat, normal QRS axis, and evidence of bi-atrial enlargement. The initial TTE was remarkable for moderate thickening of the mitral and aortic valves, which was most prominent at the commissures of the valve leaflets, with moderately reduced mobility. The mitral subvalvular apparatus was not well visualized. The mitral valve velocity time integral demonstrated a mean pressure gradient of 16 mmHg at a heart rate of 95 beats/min, with an area of 1.1 cm^2 by 2-dimensional planimetry (**Figure 1A,** Video 1). The aortic valve area was calculated as 1 cm^2 by continuity equation, with peak velocity of 3.85 m/s, mean gradient of 36 mmHg, and dimensionless index of 0.41 (**Figure 1B,** Video 2). Left heart catheterization showed normal coronary arteries, mean aortic valve gradient of 55 mmHg, and valve area of 0.49 cm^2, consistent with severe aortic stenosis. The mitral valve mean gradient on left heart catheterization was 14.3 mmHg, with valve area of 0.98 cm^2, consistent with severe mitral stenosis. The discrepancy between echocardiographic and invasive hemodynamic assessment of the aortic valve area was likely related to an underestimation of peak velocity through the aortic valve caused by the noncoaxial beam angle of the continuous-wave Doppler through a relatively small left ventricular outflow tract (LVOT). A cardiothoracic surgery consultation recommended surgical aortic and mitral valve replacement. The patient and his guardian opted for replacement with mechanical valves because of his young age and the risk for redo valve replacement with bioprosthetic valves. The results of preoperative laboratory workup and chest radiograph were unremarkable.

MANAGEMENT

After a preoperative neurosurgical evaluation, the patient underwent surgical aortic and mitral valve replacements. Intraoperative exposure of the aortic valve demonstrated a tricuspid and rheumatic-appearing valve with calcifications at the base. The mitral valve was small and rheumatic-appearing, with

FIGURE 1 Doppler Echocardiography

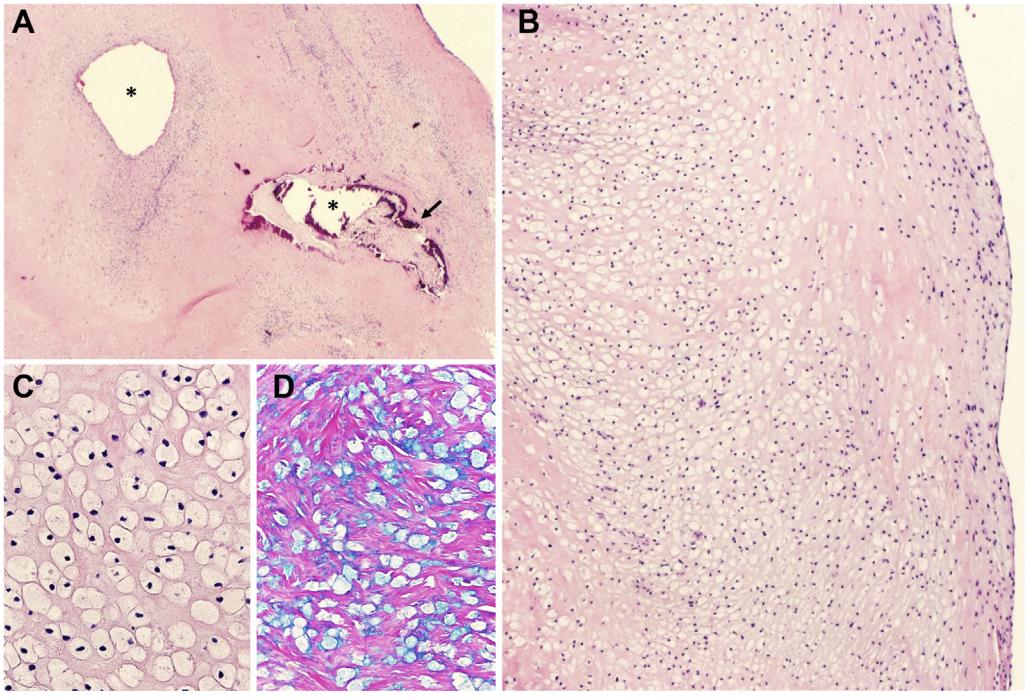


(A) Severe mitral stenosis with valve area of 1.1 cm^2 by 2-dimensional planimetry and mean gradient of 16 mmHg. **(B)** Moderate aortic stenosis with valve area of 1.0 cm^2, peak velocity of 3.85 m/s, mean gradient of 36 mmHg, and dimensionless index of 0.41.

prominent smooth-surfaced nodular areas. Both valves had no commissural fusion. A Bentall aortic root replacement with a 21-mm St Jude mechanical valve conduit was performed because of the patient's narrowed LVOT. A postoperative TTE showed an ejection fraction >55%, and normal functioning mechanical mitral and aortic valves. The patient's postoperative course was complicated by 1 episode of atrial fibrillation with rapid ventricular response, which converted back to normal sinus rhythm spontaneously. He was given warfarin for anticoagulation and was discharged home.

Histopathologic examination of the valve leaflets revealed prominent nodular fibrosis and calcification (**Figure 2A**). Diffuse transmural infiltrates of macrophages with abundant foamy cytoplasm were seen on closer inspection (**Figures 2B and 2C**). Colloidal iron cytochemical staining confirmed marked glycosaminoglycan (GAG) accumulation in the macrophage cytoplasm and valve stroma (**Figure 2D**). These findings prompted a medical genetics consultation for

FIGURE 2 Valve Histologic Features



(A) Nodular fibrosis and dystrophic calcification **(arrow)** with central degeneration **(asterisks)** were seen, along with **(B, C)** transmural infiltrates of foamy macrophages containing accumulated glycosaminoglycans, **(D)** highlighted in **blue** by colloidal iron stain.

possible mucopolysaccharidosis (MPS). Urine GAG analysis revealed elevated keratan sulfate and dermatan sulfate, supporting the diagnosis of MPS. Serum enzyme activity assays showed undetectable levels of the lysosomal enzyme α-L-iduronidase, and targeted germline sequencing identified bi-allelic variants in the *IDUA* gene, confirming a diagnosis of MPS type I.

DISCUSSION

Mucopolysaccharidoses are a family of lysosomal storage disorders caused by deficiencies in enzymes required for breakdown and turnover of GAGs. As a result, these large sugar molecules essential for connective tissue stability accumulate in blood, fluids, and tissue sites throughout the body (1). Patients with MPS have a broad spectrum of manifestations, which can include cerebral atrophy and cognitive dysfunction, tracheal and esophageal stenosis, joint stiffness and contractures, and both structural and conductive heart disease (1). Mucopolysaccharidosis type I is caused by α-L-iduronidase deficiency resulting from mutations in the *IDUA* gene inherited in an autosomal-recessive fashion. Classic MPS type I, also called Hurler syndrome, is particularly severe, often causing death in untreated patients before their teenage years (2). Scheie syndrome is a milder form of MPS type I characterized by central nervous system (CNS) sparing with primarily peripheral involvement, often leading to later diagnoses and longer life spans (2). Our patient's genetic profile may explain his unique phenotype and longevity. He was compound heterozygous for the canonical variant seen in Hurler syndrome (p.Trp402*) and in a less common variant (p.L238Q) reported in a series of adolescent and young adults presenting with intellectual disability, psychiatric illness, and hydrocephalus (3).

To our knowledge, this is the first reported case where cardiac disease was the presenting feature in an adult with a diagnosis of MPS type I. Cardiac abnormalities are common in patients across the spectrum of MPS I, but they occur later in the disease course and are rarely the cardinal feature leading to diagnosis (4). More than 80% of patients across multiple MPS type I cohort studies had evidence of cardiac dysfunction in the form of valve thickening and dysfunction or hypertrophic

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cardiomyopathy (4-6). As described by Braunlin et al (4), valves become thickened and cartilage-like, with shortened chordae and hypertrophic papillary muscles, all contributing to valve dysfunction. In 1 study of adults with attenuated MPS type I, 5 of 9 patients had mitral and/or aortic valve thickening, with all exhibiting mild or moderate valve insufficiency (7). Aortic and mitral stenosis is less common, particularly severe stenosis requiring valve replacement (8). Given such high rates of cardiovascular complications, involvement by cardiology is a critical component of optimal multidisciplinary care in MPS patients.

FOLLOW-UP

Follow-up TTE showed normally functioning mechanical valves. The patient has been closely followed up by the medical genetics service and has begun recombinant enzyme replacement therapy. Although this therapy will not diminish CNS progression, he has shown some reduction in peripheral symptoms, and his caregiver has reported significant improvement in his quality of life.

CONCLUSIONS

We describe a unique presentation and diagnosis of mucopolysaccharidosis type I. This case illustrates the importance of maintaining high clinical suspicion for systemic disease causing valvular pathologic changes in patients with unexplained neurologic or musculoskeletal symptoms, and of promptly referring such a patient to medical genetics if MPS is suspected.

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

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KEY WORDS echocardiography, genetics, inherited metabolic disorders, valve replacement

APPENDIX For supplemental videos, please see the online version of this article.