Severe Sequelae Of Subacute Bacterial Endocarditis In A Young Man With Bicuspid Aortic Valve And Marfanoid Habitus

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ABSTRACT

Patients with bicuspid aortic valve (BAV) insufficiency are uniquely predisposed to developing infective native valve endocarditis. We present an unusual case of the severe sequelae of subacute bacterial endocarditis in a patient with chronic BAV insufficiency. This case illustrates the importance of elevated clinical suspicion in patients with predisposing factors, and the potentially devastating consequences of a missed diagnosis of infective endocarditis. The patient is a 29-year-old male with Marfanoid habitus and BAV with moderate aortic insufficiency who presented with subacute Streptococcus viridans endocarditis one month after atraumatic splenic rupture. He developed severe aortic insufficiency and heart failure, which required valve replacement and debridement of endocarditic lesions. He also suffered multiple septic emboli to the brain. This case manifests an unusual constellation of severe sequelae of BAV subacute bacterial endocarditis after a possibly missed diagnosis on two prior presentations to healthcare facilities, which illustrates the importance of high clinical suspicion in patients with a predisposition to infective native valve endocarditis. The patient’s Marfanoid habitus and aortic root dilatation also highlight the growing evidence for a common pathophysiology between BAV and connective tissue disease.

INTRODUCTION

Bicuspid aortic valve (BAV) is the most common congenital cardiac anomaly in adults, estimated to be present in approximately 0.5-2% of the general population.1,2 BAV is the congenital cardiac anomaly with the highest frequency of adverse events, compared with all other congenital heart diseases combined.3 These adverse events include aortic valve dysfunction, infective endocarditis, ascending aortic aneurysm, and aortic dissection. Among the possible outcomes within this population, infectious endocarditis (IE) is an important cause of mortality, prolonged hospitalization, surgical intervention, and impaired quality of life.4 We present a case of a young man with multiple IE risk factors, including known BAV, aortic valve regurgitation, and suspected connective tissue pathology (Marfan syndrome). IE likely went undetected for months, despite multiple symptoms and signs. This case is a rare illustration of multiple adverse events in a single patient, indicating...
the need for increased vigilance for the various manifestations of endocarditis in patients with BAV. In addition, there is a growing body of evidence supporting a role for connective tissue pathology as the underlying etiology of BAV. This patient exhibited some features of Marfan syndrome, illustrating the possible intersection between BAV and connective tissue diseases.

**CASE PRESENTATION**

A 29-year-old male with Marfanoid habitus, congenital bicuspid aortic valve (BAV), and chronic moderate aortic insufficiency presented with a sudden onset low-grade fever, rigors, headache, and epigastric pain one month after suffering atraumatic splenic rupture.

Seven weeks prior to current presentation, he presented to an urgent care facility for left upper quadrant abdominal pain. White blood cell (WBC) count was 7,200 cells/µL. No imaging was performed at the time. He was discharged with opioid medication for presumed nephrolithiasis. Three weeks later, he presented to an outside hospital with sudden onset severe left upper quadrant pain. WBC count was 14,000 cells/µL. Abdominal CT revealed splenic rupture, and splenectomy was performed. Pathology revealed an atraumatic spontaneous splenic rupture with acute splenic infarct, splenomegaly, and chronic passive congestion. Monospot was negative. He was given the pneumococcal polysaccharide vaccine Pneumovax 23 (Merck&Co., Inc., Kenilworth, NJ) and discharged on the 5th post-operative day.

He presented to Maine Medical Center one month following that hospitalization with a one day history of low-grade fevers, chills, rigors, headache, and epigastric pain. Blood cultures were drawn and he was discharged from the emergency department. The following day, the blood cultures grew *Streptococcus viridans*; he was called in from home and admitted to the inpatient internal medicine service. The patient denied any recent infection, sick contacts, travel, or animal or insect bites. His last dental procedure had been a tooth extraction one year prior to presentation; he had no history of dental infection or more recent dental or oral pathology. Past medical history was significant for congenital BAV with chronic moderate aortic insufficiency, aortic root dilatation to 4.4 cm, and hypertension. Additionally, outpatient work-up for asymmetric polyarthralgia and suspected Marfan syndrome was ongoing. His only home medication was atenolol (25 mg daily) for hypertension. He had no known allergies. The patient lived with his parents and worked as a dishwasher, very rarely drank alcohol, and denied tobacco use and recreational drug use. Family history was noncontributory, though his father was also noted to exhibit a Marfanoid habitus. Review of systems was positive for arthralgias and dry cough in addition to the symptoms noted above. He denied chest pain and dyspnea.

Vital signs were notable for a wide pulse pressure (117/36 mmHg), tachycardia (102 beats/minute), and tachypnea (24 breaths/minute). Physical examination revealed a Marfanoid habitus. There were rales in the lung bases bilaterally. On cardiac auscultation, a grade III/VI diastolic rumble was heard loudest at the left sternal border. Water-hammer carotid and peripheral pulses were observed, and Quincke’s sign was present in the fingernails. Neurological exam was unremarkable. No Osler nodes, Janeway lesions, pectus deformity, scoliosis, or highly arched palate were noted. His WBC count was 32,800 cells/µL, with 96% polymorphonuclear cells. Blood cultures were positive for pan-sensitive *Streptococcus viridans*. A transthoracic echocardiogram revealed: 1) a severely dilated left ventricle with mild systolic dysfunction and global hypokinesis, 2) BAV
with anterior-posterior arrangement and raphe on the anterior leaflet, 3) multiple large vegetations on the BAV (one measuring 2.4 cm on the posterior leaflet and a second measuring 1.1 cm on the anterior leaflet), and 4) severe aortic regurgitation with no significant stenosis. The aortic root was moderately dilated to 4.6 cm at the sinuses of Valsalva. The ascending aorta was mildly dilated to 3.9 cm in the mid segment. Chest X-ray revealed diffuse interstitial prominence and small pleural effusions consistent with congestive heart failure.

Empiric antibiotic therapy (intravenous vancomycin, cefpime, and gentamicin) was initiated. Over the following day he had several hypotensive episodes with a wide pulse pressure, but otherwise remained stable. Antibiotic therapy was narrowed to intravenous ceftiraxone. Brain magnetic resonance imaging (MRI) was performed on hospital day 2 due to a complaint of headache. Multiple small acute infarcts were found within the right caudate head, right and left internal capsules, and left cerebellum. Neurological exam remained normal. Also on hospital day 2, he reported new onset dyspnea at rest and mild substernal chest pressure. On hospital day 3, ascending aortic and aortic valve replacement with homograft was performed. Intraoperatively, endocarditic lesions measuring 1.5 cm and 1.8 cm were found on the cusps of the BAV. Additional endocarditic lesions requiring debridement were identified on the anterior leaflet of the mitral valve and in the wall of the aorta. Panoramic dental radiograph performed on hospital day 5 revealed two impacted mandibular molars, but no evidence of abscess or significant decay. The patient recovered well and was discharged home.

**DISCUSSION**

BAV is the most common congenital cardiac anomaly in adults, with prevalence in the general population estimated at 0.5-2%.\(^1\)\(^,\)\(^6\) The genetics of BAV is complex, but recent evidence and linkage analysis indicates that the genes involved may also underlie other congenital anomalies of the left ventricular outflow tract.\(^6\) 80% of BAV cases are sporadic, but complex inheritance in large families has been observed.\(^6\) A high proportion (14.6%) of first-degree relatives of patients with BAV are also affected, although inheritance pattern remains unknown.\(^7\)

BAV may be detected on cardiac auscultation, with an ejection murmur best heard at the apex. Diagnosis is confirmed with transthoracic or transesophageal echocardiogram.\(^1\) Presentation of BAV varies, but BAV is typically asymptomatic until adulthood. However, infants with severe aortic stenosis may present with cyanosis or heart failure.\(^8\) BAV IE presents commonly in younger adults in the fourth decade with a strong male predominance.\(^9\) Initial manifestations may be aortic stenosis or incompetence, aortopathy, or complications\(^1\) including IE, aortic root dilatation, and heart failure. BAV endocarditis occurs at a rate of 2% in adults with BAV, regardless of the extent of aortic valve dysfunction (stenosis or regurgitation).\(^6\) Patients with regurgitation from BAV, such as the patient in this report, tend to die at a younger age and to have an increased rate of surgical intervention compared to those with BAV stenosis.\(^9\) In patients with BAV and moderate or severe aortic regurgitation (such as our patient), the frequency of cardiac events requiring medical or surgical intervention is 18% over 10 years.\(^6\) Risk factors for adverse cardiac events in patients with BAV are age >30 years, moderate or severe aortic stenosis, and moderate or severe aortic regurgitation.\(^6\)
BAV is a significant risk factor for IE of the native aortic valve, and consequences of BAV IE may be severe. In a retrospective study of patients with aortic valve IE, 16.2% had an incidental discovery of BAV, with heart failure developing in 72% of those with BAV IE. IE is the cause of >50% cases of severe aortic regurgitation in patients with BAV; these patients have a high incidence of mortality without surgery. Those with BAV IE who undergo surgery often have more severe perivalvular lesions, which are a risk for multi-organ failure. The etiology of these perivalvular lesions, which is poorly understood, may be caused by intrinsic aortic wall abnormalities. Streptococcus viridans may account for almost half of BAV infections, and dental work within 3 months of IE development predisposes to Streptococcus viridans IE. However, Streptococcus viridans IE may occur up to 24 months after a dental procedure.

As our patient’s last dental procedure had been a year prior to presentation, it is possible that IE had been present for 12 months before diagnosis. He had been evaluated within the several months prior to presentation by his primary care provider for asymmetric polyarthralgias, which may have been reactive arthritis due to undiagnosed IE. Additionally, his left upper quadrant abdominal pain seven weeks prior to presentation and atraumatic splenic rupture may have represented the results of septic emboli. With abundant evidence of predisposition to IE in patients with BAV, increased vigilance for IE at the time of those visits may have been indicated.

In addition to his BAV, the patient was noted to have a Marfanoid habitus, thoracic descending aortic aneurysm, and dilated aortic root. Marfan syndrome classically arises from a defect in fibrillin gene inherited in an autosomal dominant pattern. Its syndromic effects are outlined in the Ghent criteria, and include distinctive body habitus (reduced upper to lower segment ratio, increased arm span to height ratio, wrist to thumb signs), scoliosis, ectopia lentis, pes planus, joint hypermobility, history of spontaneous pneumothorax, and multiple cardiovascular abnormalities. Cardiovascular features of Marfan syndrome include aortic dissection and dilatation of the ascending aorta, descending thoracic or abdominal aorta, or main pulmonary artery. Diagnosis of Marfan syndrome requires involvement of two of the above organ systems with involvement of a third organ system; the patient in this report met these criteria.

There is growing evidence for connective tissue pathophysiology in BAV and its sequelae, independently of concomitant hemodynamic abnormalities. Patients with BAV are at higher risk for aortic root dilatation. Aortic root dilatation increases the risk of pathology of the thoracic aorta and valvular complications (including endocarditis and severe decompensation). In patients with BAV and dilated proximal ascending aorta, measures of vascular function indicate that there is systemic functional and structural vascular involvement. In addition, the rate of proximal aortic media elastic fiber loss is significantly higher in BAV insufficiency than in BAV stenosis; this difference may represent an independent type of aortopathy in patients with BAV insufficiency, such as our patient. Cystic medial necrosis has been demonstrated in many patients with BAV, including those with nondilated aortas. There is also a higher prevalence of BAV in patients with a dilated aortic root; this abnormality is related to congenital developmental defects of the aorta and the aortic wall. Patients with BAV and aortic regurgitation without Marfan syndrome have been found to have fibrillin-1 gene mutations, illustrating a possible common pathophysiology. Furthermore, neonatal fibrillin underproduction, especially during valvulogenesis, contributes to de-
velopment of BAV. In both Marfan syndrome and BAV, there is alteration in the amount and quality of secreted proteins such as fibronectin and increased rates of apoptosis, suggesting a generalized cellular transport mechanism defect. Although this patient’s workup for Marfan syndrome is ongoing, his case embodies the intersection between connective tissue disease and BAV.

This patient possessed multiple risk factors for IE, specifically chronic aortic insufficiency, aortic root dilatation, and possible connective tissue disorder. The patient’s atraumatic splenic rupture one month prior to presentation was at the time believed to be idiopathic. However, the splenic infarct and rupture may have been caused by emboli from undiagnosed infectious endocarditis, especially in light of his elevated WBC count at that time. While splenic infarct is a known complication of IE, patients with IE rarely present with atraumatic splenic rupture. In a systematic review of the etiologies of atraumatic splenic rupture, only 16 patients out of 926 (1.7%) had rupture secondary to bacterial endocarditis. In a series of abdominal CT scans performed on 29 asymptomatic patients with endocarditis, 38% had unrecognized splenic infarcts. IE may also cause splenic aneurysm and abscess. It is possible that our patient’s left upper quadrant abdominal pain and presumed nephrolithiasis may have represented occult splenic infarct related to undiagnosed IE (the patient did not pass a stone, and there is no evidence that nephrolithiasis occurred). Further workup at the time of his presumed nephrolithiasis was not indicated. However, despite the patient’s risk factors, leukocytosis, and negative Monospot, further workup for the etiology of splenic rupture was not performed at the time of splenectomy. If diagnostic workup for IE had been performed at that time, echocardiogram may have revealed endocarditic lesions, or blood culture may have grown *Streptococcus viridans*. Earlier detection could have allowed intravenous antibiotic therapy to be started, potentially avoiding a repeat hospitalization, multiple emboli to the brain, and surgical intervention. The effects on the patient’s wellbeing and the health care costs incurred are significant.

There are, however, limitations to these conclusions. Based on clinical reasoning, the size of the endocarditic lesions, lack of dental pathology at the time of presentation, and the typical subacute time course of *Streptococcus viridans* IE, we have extrapolated that IE caused the symptoms and signs described above. However, we cannot exclude with absolute certainty other causes of polyarthralgia, LUQ abdominal pain, and splenic rupture. The yield for performing echocardiogram in all patients with BAV who present with abdominal pain would be prohibitively low. It is only with the constellation of this patient’s manifestations, and presentations to different providers, that the diagnosis of IE becomes clear. It is therefore important for primary care providers to have elevated suspicion in order to synthesize the apparently unrelated problems. Additionally, despite meeting Ghent criteria for clinical diagnosis of Marfan syndrome, outpatient workup for Marfan syndrome continues. The patient has not yet undergone genetic testing.

This unusual case illustrates the potentially severe complications of IE in a young man with chronic BAV insufficiency and possible Marfan syndrome, and the importance of vigilance in patients with BAV. He developed *Streptococcus viridans* IE without significant dental or oral pathology. The patient’s repeated visits to outside facilities for polyarthralgia, left upper quadrant pain, and splenic rupture in the weeks leading up to his presentation may have represented missed opportunities to diagnose IE. By the time he presented to our hospital, the patient had multiple large vegetations and endocarditic lesions involving the mitral valve, BAV, and aorta. He had received annual surveillance trans-
esophageal echocardiograms, per current guidelines for known BAV. The last echocardiogram was before his symptoms arose. Early diagnosis could have potentially avoided his constellation of sequelae, including splenic infarct and rupture, multiple cerebral infarcts (although without detectable neurologic deficits), severe aortic insufficiency, congestive heart failure requiring aortic valve and ascending aorta replacement with homograft, and significant hospital stay.

**REFERENCES**


**LEARNING POINTS**

- In patients with BAV insufficiency uniquely predisposed to IE, it is important to maintain a higher index of clinical suspicion to lead to earlier diagnosis and treatment.

- BAV IE can have potentially disastrous sequelae affecting multiple systems in a single patient.

- The concurrence of Marfanoid habitus with BAV and a history of significant aortic root dilatation embodies an example of the growing evidence for connective tissue pathology in patients with BAV insufficiency.

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