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VASCULAR MEDICINE

CASE REPORT: CLINICAL CASE

Treponema Pallidum

A Forgotten Pathogen With Major Cardiovascular Consequence

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ABSTRACT

The incidence of syphilis has increased in the last 2 decades. This case describes a 43-year-old with aortic aneurysm and symptomatic aortic regurgitation initially suspected to be congenital and later confirmed as syphilitic in etiology, illustrating a growing need to consider tertiary syphilis as a cause of aortopathy. (JACC Case Rep. 2024;29:102575)
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HISTORY OF PRESENTATION

A 43-year-old male patient with a large thoracic aortic aneurysm (maximal diastolic dimension of 6.7 cm, involving both the aortic root and ascending limb), moderate functional aortic regurgitation, non-ischemic cardiomyopathy, and heart failure (HF) with severely reduced left ventricular ejection fraction (LVEF) (<20% on prior transthoracic echocardiogram [TTE]) with primary prevention implantable cardioverter-defibrillator was referred to our center for refractory HF symptoms. During his initial visit, he endorsed a history of prior methamphetamine use, long-standing human immunodeficiency virus infection with intermittent compliance with antiretroviral therapy, and late latent syphilis with progression to ocular syphilis several months prior. Furthermore, he had been previously evaluated for surgical aortic repair at an outside center but ultimately declined due to his severely reduced systolic function and concern for active methamphetamine use at the time.

LEARNING OBJECTIVES

- To recognize the increasing incidence of syphilis in the United States in the last 2 decades.
- To understand the spectrum of cardiovascular manifestations that may arise from tertiary syphilis, which will likely be of increasing prevalence alongside the growing number of syphilitic infections.

PAST MEDICAL HISTORY

The patient was first diagnosed with syphilis 4 years prior, although it was not known if he was treated at the time. One year prior to presentation, he was diagnosed with late latent syphilis with a rapid plasma reagin (RPR) of 1:8 dilutions; however, he completed only 1 of 3 prescribed doses of intramuscular penicillin. Several months prior to our evaluation, he was admitted for new onset HF at which time his RPR was 1:2. During this admission, he reported subacute vision changes, and ophthalmologic

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ABBREVIATIONS AND ACRONYMS

HF = heart failure

LVEF = left ventricular ejection fraction

RPR = rapid plasma reagin

TTE = transthoracic echocardiography

examination revealed a left-sided fourth cranial nerve palsy, as well as rare vitreous cells, a nonspecific finding for inflammation. In consultation with infectious diseases and ophthalmology, he was treated with intravenous penicillin for 14 days given concern for ocular syphilis.

DIFFERENTIAL DIAGNOSIS

The patient's large aortic aneurysm and cardiomyopathy were notable given their severity alongside his relatively young age. He reported a family history of HF with several second- and third-degree relatives with HF diagnosed in the fourth and fifth decades of life with unknown aortic involvement. Given these findings, we approached his aortopathy by first considering nonsyndromic genetic mutations associated with familial thoracic aortic aneurysm (eg, *TGFBR2*, *MYH11*, *ACTA2*). He had no other clinical features to suggest a connective tissue disease associated with aortic aneurysm or other autoimmune disease. Furthermore, while syphilitic aortitis was considered given his history, the unclear duration of his syphilis infection called this diagnosis into question.

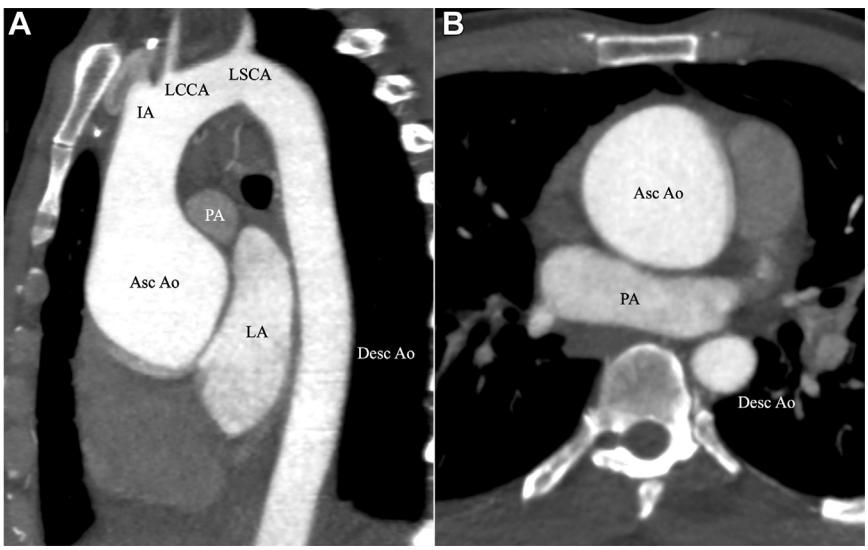
INVESTIGATIONS

Coronary computed tomography angiography demonstrated his known aortic aneurysm with no coronary artery disease (Figure 1). Cardiac magnetic resonance confirmed a trileaflet aortic valve morphology. Right heart catheterization demonstrated low-normal intracardiac filling pressures with normal cardiac output (4.92 L/min, indexed to 2.43 L/min/m^2). Genetic testing for variants associated with familial cardiomyopathies and aortopathies returned positive for variants of unknown significance: *ALPK3* variant c.2197 C>T (p.Arg733Trp) and *LTBP3* variant c.2854 G>A (p.Asp952Asn). Last, a TTE was repeated, which revealed a severely increased left ventricular internal diameter at end-diastole of 7.1 cm, interval improvement in his LVEF to 40% to 45%, and progression to severe aortic regurgitation (effective regurgitant orifice area of 0.65 cm^2 with a regurgitant volume of 194 mL).

MANAGEMENT

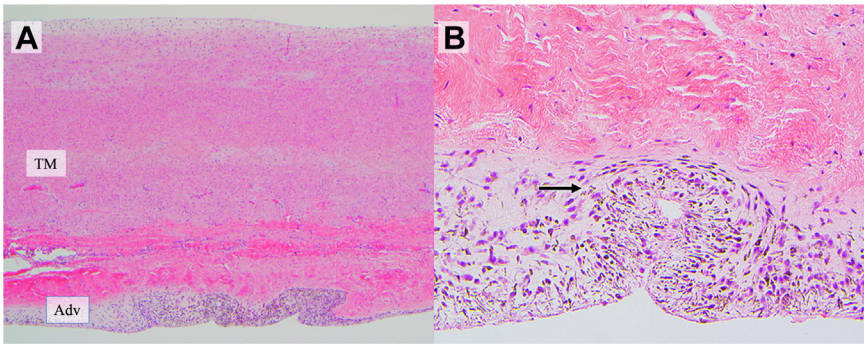
Given the LVEF improvement and progression to severe aortic regurgitation, the patient was evaluated by the heart team in consultation with clinical social work and was deemed acceptable for surgery.

FIGURE 1 Imaging Assessment of the Aorta



Computed tomography angiography images showing a large aneurysm of the aortic root and ascending aorta (Asc Ao) measuring 6.7 cm in diastole, shown in (A) sagittal multiplanar reconstructed and (B) axial views. Desc Ao = descending aorta; IA = innominate artery; LA = left atrium; LCCA = left common carotid artery; LSCA = left subclavian artery; PA = pulmonary artery.

FIGURE 2 **Histological Evaluation of the Aorta**



Ascending aortic aneurysm excision showing severe medial degeneration with adventitial fibrosis and hemosiderosis (arrow) consistent with healed arterial injury: hematoxylin and eosin stain, (A) ×4 and (B) ×20 magnification. Adv = adventitia; TM = tunica media.

The patient underwent successful ascending aortic aneurysm repair in addition to aortic valve replacement with a 27 mm Magna Ease bioprosthetic valve (Edwards Lifesciences), due to the patient's strong preference to avoid long-term oral anticoagulation. Surgical pathology revealed severe medial degeneration of the ascending aorta with adventitial fibrosis and focal areas of hemosiderosis, consistent with healed arterial injury. While not specific to an etiology, these findings are compatible with a healed syphilitic aneurysm after treatment, in which the initial inflammation and injury begins in the adventitial layer (**Figure 2**).

DISCUSSION

Syphilis, a chronic infection caused by the spirochete *Treponema pallidum*, has stood as a major cause of morbidity and mortality for centuries. Despite best public health efforts, the incidence of syphilitic infections has steadily increased over the last 20 years, with more than 133,000 new cases diagnosed in the United States in the year 2020, particularly among men who have sex with men.[1] After completion of highly variable primary and secondary stages of infection (reviewed elsewhere),[2,3] as many as one-third of patients progress to develop some form of tertiary syphilis with cardiovascular, gummatous, or neurologic manifestations.[2]

In the pre-antibiotic era, cardiovascular complications of late syphilis were once a common finding at time of death, with up to 7% incidence in one series of 15,000 consecutive autopsies from 1927 to 1937.[4] These early postmortem series and others that followed reveal the breadth of cardiovascular complications of syphilis, comprising largely aortitis and its associated complications: aortic aneurysm, aortic regurgitation, and coronary ostial stenosis. Syphilitic aortitis may develop within 10 to 30 years after primary infection, with uncomplicated aortitis affecting as many as 70% to 80% of untreated patients.[5,6] A notable feature of syphilitic aortitis is its involvement of only vessels containing vasa vasorum, possibly stemming from the hematogenous spread of *T pallidum* to vasa vasorum during early phases of infection. For this reason, syphilitic aortitis is confined to regions of the thoracic aorta and spares the abdominal aorta and coronary arteries.[7] Histologically, there is progressive fibrosis and thickening of the aortic adventitia (containing vasa vasorum) with resultant degeneration of smooth muscle cells and elastic fibers in the media. The weakened vessel wall may form fusiform or saccular aneurysmal segments in regions of aortitis, which rarely may involve the entire thoracic aorta.[7,8] Furthermore, large aneurysms may be complicated by the formation of mural thrombus or vessel rupture.[9] In cases of proximal aortic involvement, syphilitic aortitis may cause aortic regurgitation by aortic root dilatation (as seen in our case) or by primary valvular involvement with cusp deformation.[9] These changes may be accompanied by valvular cardiomyopathy or symptoms of HF. Adventitial inflammation and fibrosis of the aortic root may lead to progressive stenosis of one or both coronary artery orifices, with the potential for obstruction and anginal symptoms[7,9] Last, gummatous involvement of the myocardium has been described to cause conduction disease including complete heart block, although this is seldom reported.

The irreversible nature of cardiovascular complications in syphilis necessitates early recognition and treatment with antimicrobial therapy and surgical intervention as appropriate. Current Centers for Disease Control and Prevention guidelines recommend treating tertiary syphilis, including those with cardiovascular manifestations, with 3 weekly doses of benzathine penicillin G (2.4 million units intramuscularly each dose).[10] As *T pallidum* cannot be cultured clinically, nontreponemal serologic tests (eg, RPR) are used to demonstrate a 4-fold decline in titers, suggesting treatment response.

FOLLOW-UP

The patient had an unremarkable postoperative course. A postoperative TTE revealed an improved left ventricular internal diameter at end-diastole (6.1 cm, from 7.1 cm preoperatively), LVEF of 40% to 45%, and no central or paravalvular aortic regurgitation. The patient was discharged on postoperative day 10. One month after surgery, the patient reported a significant improvement in his symptoms upon follow-up in clinic.

CONCLUSIONS

The increasing incidence of syphilis in the United States will likely be mirrored by a similar increase in cardiovascular complications relating to untreated infection. Timely recognition and treatment of syphilitic infections is essential to prevent cardiovascular sequelae.

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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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