CLINICAL PROBLEM-SOLVING

Caren G. Solomon, M.D., M.P.H., *Editor*

The Young and the Breathless

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In this Journal *feature, information about a real patient is presented in stages (boldface type) to an expert clinician, who responds to the information by sharing relevant background and reasoning with the reader (regular type). The authors' commentary follows.*

A previously healthy 18-year-old woman presented to a primary care provider with a 2-month history of headaches and midscapular pain. The midscapular pain was worse at rest, particularly at night, and lessened with exercise. Symptoms began after a low-speed motor vehicle collision and 2 weeks after she had received a messenger RNA vaccination against coronavirus disease 2019 (Covid-19). The heart rate was 85 beats per minute, blood pressure 114/65 mm Hg, and body temperature 36.7°C. Approximately 12 oral ulcers were noted on the tongue and buccal mucosa. Musculoskeletal and cardiopulmonary examinations were unremarkable. Given the patient's 10-year history of intermittent herpes stomatitis, an empirical course of acyclovir was prescribed. Naproxen and physical therapy were recommended for back pain.

Although back pain is a nonspecific finding, nocturnal pain is not typically associated with muscle strain and may portend a more serious cause. Oral ulcerations in this patient are most likely due to herpes simplex virus (HSV) infection, but they may also be a manifestation of a range of diseases, including systemic lupus erythematosus, reactive arthritis, Behçet's disease, inflammatory bowel disease, celiac disease, dermatologic processes (e.g., autoimmune bullous disease), and human immunodeficiency virus infection. The relevance of recent Covid-19 vaccination is uncertain, although there have been anecdotal reports of oral ulcerations after immunization.

The patient's back pain did not abate and migrated from the mid-back to the lower back, and recurrent low-grade fevers developed, which prompted referral to a rheumatology clinic, where she was evaluated 2 months after the initial presentation. She reported no ocular pain, vision changes, abdominal pain, diarrhea, hematochezia, or history of venous or arterial thrombosis. She had been adopted and was unable to provide family history. Examination revealed no synovitis or rash. A vaginal ulceration that was similar to her oral ulcerations had developed in the interim. Inflammatory spondyloarthritis was thought to be an important diagnostic consideration, and laboratory studies were performed, with results including a normal complete blood count and metabolic panel, an erythrocyte sedimentation rate (ESR) of 100 mm per hour (normal value, ≤20), a serum C-reactive protein (CRP) level of 102 mg per liter (normal value, ≤10), negative antinuclear antibody screening, and a negative antineutrophil cytoplasmic antibody panel. Results of additional testing during the next several months included an HSV type 1 (HSV-1) IgG antibody level of 50.30 units (normal value, <0.91), positivity for tissue transglutaminase (tTG) anti-

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body and deamidated gliadin antibodies, and normal serum complement levels. Testing was negative for HLA-B27 and HLA-B51 and for a panel of 15 antibodies associated with myositis. Magnetic resonance imaging (MRI) showed no evidence of sacroiliitis. Upper endoscopy, performed owing to the elevated tTG level, showed *Helicobacter pylori* but no evidence of celiac disease. The *H. pylori* infection was treated, and a gluten-free diet was started for possible gluten sensitivity.

The patient's persistent symptoms and markedly elevated CRP level and ESR are suggestive of a systemic inflammatory disorder. The absence of evidence of sacroiliitis argues against spondyloarthritis but does not rule it out. Behçet's disease, an idiopathic multisystem vasculitis, could cause the oral and genitourinary ulcerations as well as constitutional symptoms. Contrary to the strong relationship between HLA-B27 and ankylosing spondylitis, HLA-B51 is only modestly associated with Behçet's disease, with low positive and negative predictive values. The elevated HSV-1 IgG antibody level indicates previous HSV infection but does not inform whether recent ulcerations were due to this infection.

Six months after symptom onset and several weeks before scheduled outpatient follow-up, the patient presented to the emergency department with a 2-week history of progressive dyspnea on exertion and chest tightness. The patient's body temperature was 37.1°C, heart rate 107 beats per minute, blood pressure 98/61 mm Hg, respiratory rate 15 breaths per minute, and oxygen saturation 99% while she was breathing ambient air.

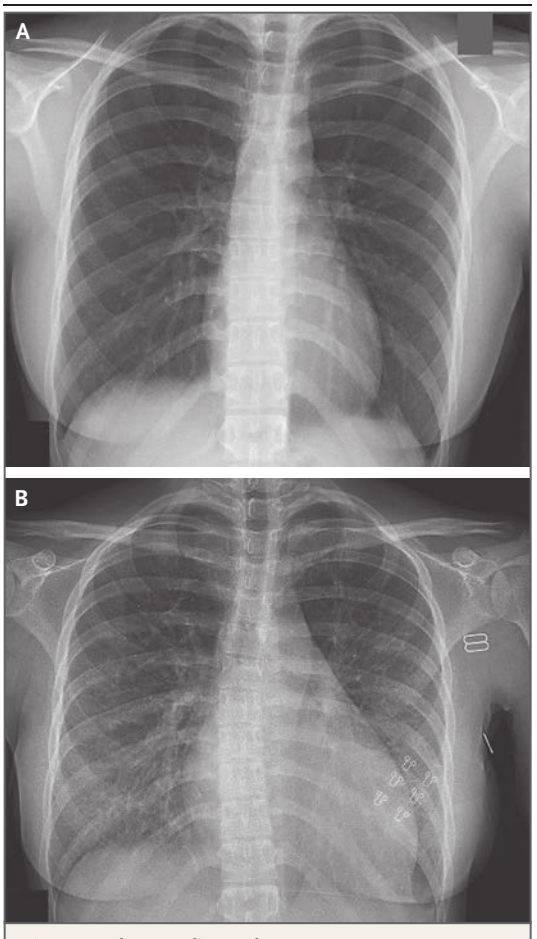

Figure 1. Chest Radiographs.
As compared with a normal previous posteroanterior chest radiograph (Panel A), the anteroposterior radiograph that was obtained at presentation (Panel B) showed increased interstitial markings and new cardiomegaly, even with differences in technique taken into account.

The differential diagnosis for this acute presentation is broad and includes pulmonary embolism and other pulmonary disease, anemia, and cardiovascular causes, including coronary disease, myocarditis, pericarditis, and valve dysfunction. With a 2-week history, an acute coronary event, such as dissection or coronary spasm, is unlikely, although heart failure occurring several days after the acute event is possible. Endocarditis can manifest with a prolonged subacute course, followed by more rapid deterioration when valve dysfunction supervenes. However, recurrent fevers and back pain in conjunction with elevated inflammatory markers arouse concern for inflammatory aortic disease. Myocarditis or pericarditis may occur in patients with a systemic inflammatory disorder or viral infection, resulting in fevers and eventual heart failure (in the latter case from constrictive physiological features after pericarditis).

The physical examination was notable for a grade 4/6 diastolic decrescendo murmur that was loudest at the left lower sternal border and for crackles in the lower and middle fields of both lungs. A bruit was present in the right supraclavicular fossa. The pulses were 2+ in the arms and legs. The patient had no oral or genital ulcers and no rash. Neurologic and musculoskeletal examinations were normal. The complete blood count,

glucose level, and electrolyte levels were normal. The serum creatinine level was 1.07 mg per deciliter (95 μmol per liter), as compared with a baseline level of 0.69 mg per deciliter (60 μmol per liter). The serum troponin I level was 0.05 ng per milliliter (normal value, ≤0.04), the B-type natriuretic peptide level 2484 pg per milliliter (normal value, ≤101), the D-dimer level 0.96 μg per milliliter (normal value, ≤0.59), the ESR 19 mm per hour, and the CRP level 41.9 mg per liter. A chest radiograph showed cardiomegaly and increased interstitial markings, both new as compared with a study obtained 8 months earlier at the time of the motor vehicle collision (Fig. 1).

The examination is consistent with aortic regurgitation due to either aortic-valve disease or pathologic features in the ascending aorta. Although a long-standing abnormality such as congenital bicuspid aortic valve is a possible underlying cause, the normal cardiac size on the radiograph 8 months earlier suggests a more acute process.

Endocarditis is the most common cause of acute aortic regurgitation. However, mediastinal widening on chest radiography arouses concern for aortic aneurysm or dissection. Enlargement of the cardiac silhouette may reflect left ventricular dilation, but pericardial effusion complicating aortic dissection should also be considered.

Computed tomographic (CT) angiography revealed interstitial and alveolar edema without evidence of thromboembolism. The contour of the descending thoracoabdominal aorta was noted to be irregular with proximal narrowing of the superior mesenteric and celiac arteries (Fig. 2). There was no pericardial effusion.

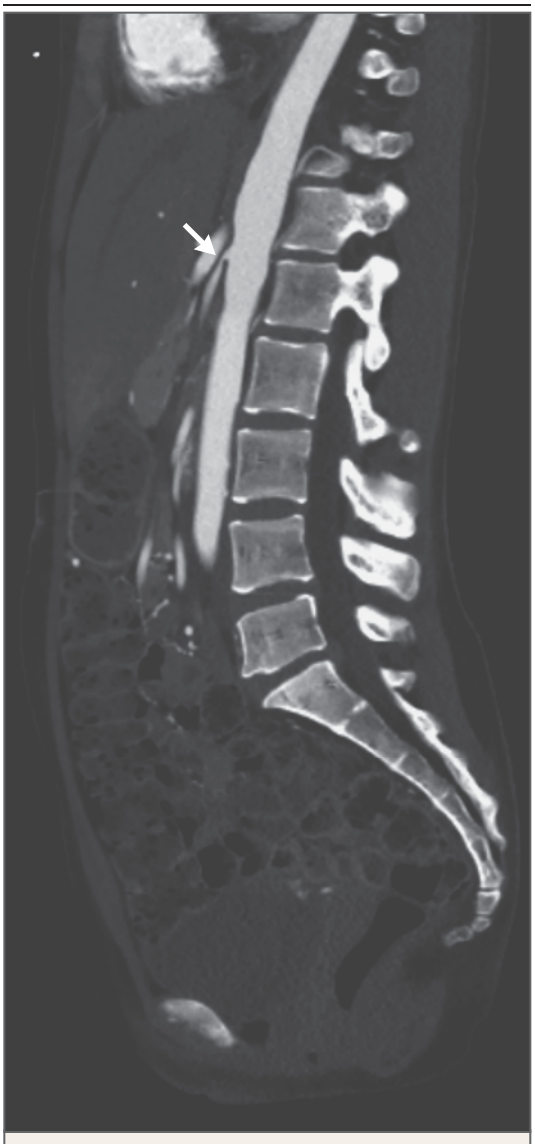

Figure 2. CT Angiography.
Shown is an irregular aortic contour with focal asymmetric and concentric narrowing as well as focal 65% stenosis of the ostial superior mesenteric artery (arrow).

CT findings suggest an inflammatory aortitis. Takayasu's arteritis, a large-vessel vasculitis that most commonly affects women younger than 40 years of age, is most likely. The differential diagnosis for aortitis also includes Behçet's disease, although vascular involvement in Behçet's disease predominantly affects men and rarely involves the aortic root or ascending aorta. Although genitourinary ulcerations are consistent with Behçet's disease, HSV infection is another plausible explanation for ulcerations in this patient. The patient also has no evidence of other findings associated with Behçet's disease, such as uveitis, neurologic manifestations, thrombosis, or synovitis, although the absence of these conditions does not rule out this diagnosis. Infectious aortitis, especially syphilitic aortitis, is less likely, given that it typically manifests in older adults as a complication of tertiary syphilis, but should be ruled out. Imaging of the valve and aorta should be performed.

Transthoracic echocardiography (Video 1, and Fig. S1 in the Supplementary Appendix, available

A video showing transthoracic echocardiography is available at NEJM.org

with the full text of this article at NEJM.org) revealed severe left ventricular dilation and reduced systolic function (ejection fraction, 37%). There was severe, anteriorly directed aortic regurgitation from a trileaflet valve, with aneurysmal dilation of the left sinus of Valsalva resulting in malcoaptation of the left coronary cusp. A regurgitant fraction of 56% was calculated with the use of the Doppler velocity–time integral. Arterial duplex ultrasonography revealed multiple focal stenoses of up to 50% in the right subclavian artery. Needle-stick testing was negative for pathergy. *Treponema pallidum* IgG and IgM antibody screening was nonreactive.

Although not definitive, the absence of pathergy (defined as the development of a sterile papule or pustule within 1 or 2 days after needle insertion) further argues against Behçet's disease. Left ventricular dilation is a maladaptive compensatory mechanism that maintains normal cardiac output despite substantial diastolic backflow and suggests that aortic regurgitation is not acute. Transesophageal echocardiography (TEE) or cardiac-gated CT with the use of contrast material should be considered in order to rule out dissection and to characterize the aortic root in anticipation of surgical intervention.

TEE confirmed severe aortic regurgitation due to a left sinus of Valsalva aneurysm. Cardiac MRI did not show a myocardial scar and confirmed severe aortic regurgitation (regurgitant fraction, 53%). ^{18}F-fluorodeoxyglucose (FDG)–positron-emission tomography (PET) and CT revealed diffuse active aortic inflammation, including at the aortic root (Fig. 3).

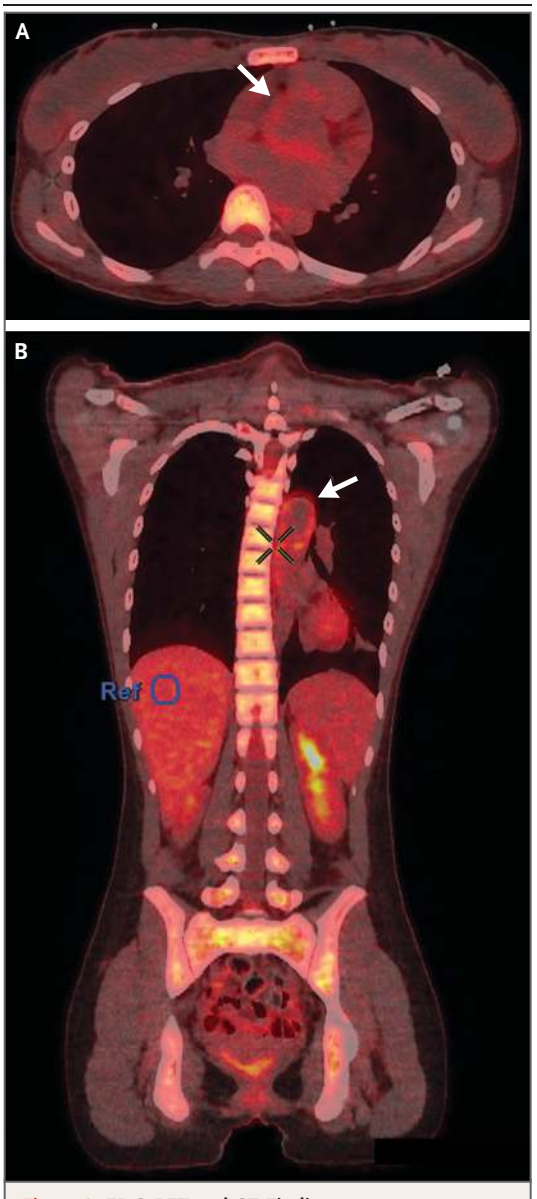

Figure 3. FDG-PET and CT Findings.
Low-dose CT images are coregistered with positron-emission tomographic (PET) data to produce the final images. ^{18}F-fluorodeoxyglucose (FDG) uptake in the aortic root and aortic arch is indicated by the arrows in Panel A (axial view) and Panel B (coronal view), respectively. Aortic FDG uptake was suggestive of active inflammation.

Takayasu's arteritis may involve any segment of the aorta and its branch vessels and commonly results in inflammation of the aortic root, which may lead to aneurysmal dilation or wall thickening. The only effective treatment for severe aortic regurgitation is restoration of valve competency, which is frequently accomplished by replacement of the valve with a prosthesis and of the diseased aorta with a graft. Other options, at experienced centers, include reimplantation of the native aortic valve within an aortic graft (e.g., the David-V technique) or replacement of the aortic valve and sinuses with the patient's own pulmonic valve along with placement of a pulmonic homograft (i.e., the Ross procedure). Retention of the native aortic valve has advantages over replacement; mechanical valves are durable but require permanent anticoagulation,

and bioprosthetic valves have limited durability in young adults and would probably necessitate reintervention within 10 years.

The clinical decision making is complex, because the inflammatory nature of the patient's aortopathy arouses concern for intraoperative complications related to tissue friability as well as the potential for later anastomotic dehiscence. Multidisciplinary consultation and initiation of antiinflammatory therapy are necessary before surgery. The reduced left ventricular ejection fraction is worrisome, but delaying intervention for a short period to allow for suppression of the inflammatory process is unlikely to increase the risk of irreversible left ventricular systolic dysfunction. Although not effective for aortic regurgitation, guideline-directed medical therapy is often effective for left ventricular systolic dysfunction. If the patient's condition is too unstable to defer intervention, surgery should be recommended after a careful risk–benefit discussion with the patient and her family.

Out of concern about perioperative complications, surgical intervention was delayed for 16 days, during which time immunosuppressive therapy was initiated, including intravenous methylprednisolone at a dose of 500 mg daily for 5 days, followed by oral prednisone at a dose of 55 mg daily (1 mg per kilogram of body weight per day) and concurrent weekly subcutaneous administration of 15 mg of methotrexate. Tumor necrosis factor α inhibitors were not used given the degree of heart failure. Medical therapy for heart failure was initiated, including sacubitril–valsartan (24 mg of sacubitril and 26 mg of valsartan twice daily) and spironolactone (12.5 mg daily). The patient strongly preferred to avoid long-term anticoagulation, so surgical valve-sparing aortic-root replacement (David-V technique) was performed with concomitant aortic-valve repair.

Pathological examination of the resected aorta (Fig. 4) showed extensive destruction of the tunica media with prominent intimal thickening and adventitial fibrosis but no active inflammation. Postoperatively, she had only mild aortic regurgitation; with guideline-directed medical therapy for heart failure, her left ventricular ejection fraction increased, and her abnormally high left ventricular volume decreased. She was discharged on hospital day 26 while receiving sacubitril–valsartan (24 mg of sacubitril and 26 mg of valsartan twice daily), spironolactone (25 mg daily), and empagliflozin (10 mg daily), with a plan to increase the doses as an outpatient.

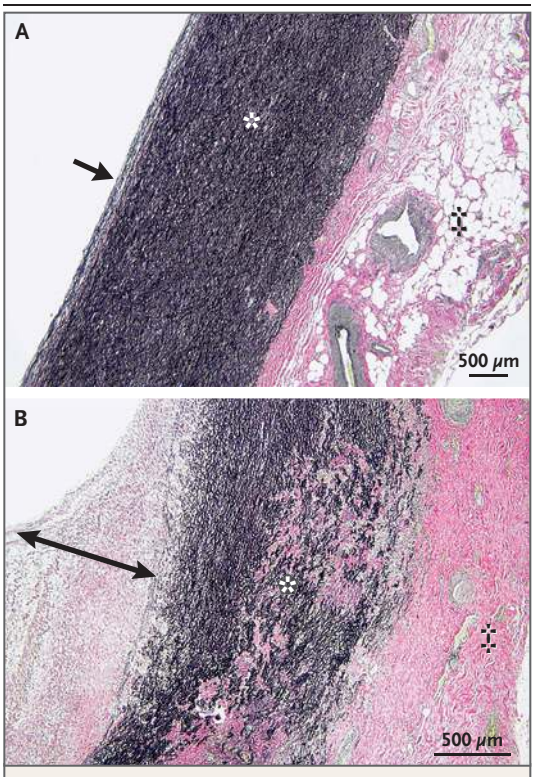

Figure 4. Representative Photomicrographs from Surgical Pathology.

Histologic analysis of surgical specimens after staining with Verhoeff–van Gieson stain to highlight elastic fibers, which are a major component of the tunica media (asterisk), showed distal segments of normal aorta (Panel A) with thin endothelium (arrow), intact tunica media, and healthy adventitia with vasa vasorum (double dagger). Proximally, there were segments of near-total destruction of elastic lamina, which was associated with prominent intimal thickening (double arrow) and adventitial fibrosis (double dagger) (Panel B).

The absence of active inflammation on pathological examination supports the idea that preoperative immunosuppressive therapy for Takayasu's arteritis was effective. Antiinflammatory therapy may be weaned or discontinued if remission occurs, but long-term monitoring with serial pulse examination, measurement of inflammatory markers, and cross-sectional imaging of the aorta and branch vessels is essential. Mag-

netic resonance angiography may be used for this purpose to reduce radiation exposure, with FDG-PET reserved for cases in which there is concern about ongoing or recurrent inflammation. Continued care by a multidisciplinary team — including a rheumatologist, a cardiologist, and a vascular surgeon — is needed.

COMMENTARY

Takayasu's arteritis, which often initially manifests as nonspecific symptoms and laboratory abnormalities, presents a diagnostic challenge. After arthralgias, fatigue, and low-grade fever had developed, our patient was found to have substantially elevated inflammatory markers. Despite an expansive workup, the diagnosis was made only after she presented in decompensated heart failure caused by severe aortic regurgitation, leading to imaging that showed inflammatory aortic-root dilation.

Takayasu's arteritis is a rare chronic inflammatory disease of the aorta and branch arteries of as-yet-unknown cause that occurs more frequently in women than in men and that often manifests before 40 years of age.[1] Estimates of prevalence vary widely, from 0.9 cases per million persons in the United States[2] to 40 cases per million in Japan.[3] Early autopsy studies in Japan indicated a prevalence as high as 1 in 3000, which supports substantial underdiagnosis.[4] Vasculitis due to Takayasu's arteritis is characterized by cell-mediated autoimmunity with infiltration by $\gamma\delta$ lymphocytes, dendritic cells, and granulocytes, although, as in this case, immunosuppression may conceal these findings, leaving only evidence of medial destruction.[5] The pathophysiology probably involves an interplay between genetics and environment. Variants in multiple loci, in the HLA region and elsewhere, have been associated with Takayasu's arteritis, but no single variant has been identified as causal.[6]

Constitutional symptoms, including fatigue, low-grade fever, night sweats, and weight loss, are frequent early manifestations of Takayasu's arteritis, occurring in up to 65% of patients in case series.[7,8] Although synovitis is rare, arthralgias are common (in approximately 40% of patients).[8] Dermatologic manifestations such as erythema nodosum or a lupus-like photosensitive malar rash may be early findings, occurring in approximately 20% of patients.[9] As the disease progresses, symptoms of large-vessel vasculitis predominate. Carotid-artery tenderness (carotidynia), arterial bruits, hypertension, discrepant blood pressure, gastrointestinal symptoms, angina, visual disturbances, and neurologic symptoms may occur, depending on the distribution of arterial inflammation and resultant stenosis.[1] In all stages, but especially in the late stenotic phase of the disease, distal pulses are often asymmetrically diminished or even absent, leading to the moniker "pulseless disease."[10]

Various diagnostic criteria have been developed, largely for research purposes.[11] The 1990 American College of Rheumatology (ACR) classification criteria for Takayasu's arteritis include the presence of at least three of six features: an age at onset of less than 40 years, claudication, decreased brachial-artery pulse, a blood-pressure difference of more than 10 mm Hg between arms, subclavian or aortic bruit, and abnormal aortic imaging. This definition is reportedly 90.5% sensitive and 97.8% specific for Takayasu's arteritis, although the age criterion has been debated given that 13 to 17.5% of patients receive a diagnosis after 40 years of age.[11]

Aortic regurgitation complicates approximately 25% of cases of Takayasu's arteritis. Malcoaptation due to dilation of the aortic root is probably the primary mechanism.[1] Severe aortic regurgitation is classically associated with an early diastolic decrescendo murmur, best heard at the left lower sternal border. Other findings include a bounding pulse with rapid systolic rising and diastolic collapse (Watson's water hammer pulse), bobbing of the head (de Musset's sign), and repeated flushing and blanching of the capillary nail beds (Quincke's pulse). Regardless of the cause, if left untreated, severe aortic regurgitation results in progressive left ventricular dilation, remodeling, systolic dysfunction, heart failure, and ultimately death; valve repair or replacement is necessary to interrupt this natural history.[12]

In the absence of randomized trials, management is largely guided by expert opinion. The mainstay of treatment is high-dose glucocorticoid therapy, followed by the addition of glucocorticoid-sparing agents.[13] ACR guidelines continue to favor azathioprine, leflunomide,

methotrexate, mycophenolate mofetil, or cyclophosphamide, on the basis of observational data.[13] However, tocilizumab, a monoclonal antibody against the interleukin-6 receptor that has proven efficacy in giant-cell arteritis, has also been used effectively.[14] In patients undergoing aortic surgery, pretreatment with immunosuppression is routinely used with the goal of reducing the risk of anastomotic dehiscence, a catastrophic complication,[15] although this approach has not been prospectively studied. The appropriate timing of surgical intervention in relation to immunosuppressive therapy is unclear, and decisions are individualized according to a patient's clinical presentation and stability.

This case highlights the diagnostic and management challenges presented by Takayasu's arteritis, an understudied and underrecognized large-vessel vasculitis. Especially in young women presenting with constitutional symptoms and elevated inflammatory markers, careful physical examination is important to screen for vascular and valvular manifestations of this elusive diagnosis.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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