

Severe Aortic Regurgitation and Left Main Coronary Artery Ostial Stenosis in a 21-Year-Old Woman: What's Going On?



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INTRODUCTION

Takayasu arteritis (TA) is a chronic, progressive, granulomatous, large-vessel vasculitis that affects mainly the aorta and its major branches. Aortic inflammation evolves to fibrosis, and artery wall scarring leads to stenosis or occlusion, while elastic lamina and muscular media destruction can lead to aneurysm formation. Significant ostial coronary artery stenosis and severe aortic regurgitation (AR) are the main indications for surgical management. We describe the case of a young woman with dyspnea and chest pain on exertion due to severe aortic insufficiency and left main coronary artery (LMCA) stenosis requiring surgical management, both related to different TA pathophysiologic mechanisms. We discuss the principles of diagnosis and management of major vascular complications in patients with this disease.

CASE PRESENTATION

A 21-year-old woman with a recent presumptive diagnosis of TA was admitted because of dyspnea on exertion (DOE) and chest pain. Her DOE progressed over time, happening initially during jogging and later on climbing two flights of stairs. In the last month, her DOE was associated with precordial, oppressive, and nonradiating chest pain with mild exertion.

On review of systems, she described syncope for the past 2 years that was interpreted as vasovagal episodes because of apparent prodromal symptoms. These episodes lasted only a few seconds, without residual symptoms or sequelae. Also, she reported arm claudication without fever, chills, weight loss, or fatigue.

Her medical history included TA diagnosed 12 months earlier. She was treated 4 weeks previously with intravenous antibiotics for a complicated urinary tract infection. Medications included prednisolone 35 mg/d, azathioprine 200 mg/d, acetylsalicylic acid 81 mg/d, and atorvastatin 40 mg/d.

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Keywords: Takayasu arteritis, Aortitis, Aortic valve insufficiency, Coronary artery disease

Conflicts of interest: The authors reported no actual or potential conflicts of interest relative to this document.

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2468-6441

<https://doi.org/10.1016/j.case.2020.09.004>

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On physical exam, the patient's vital signs were as follows: temperature 37.1°C, heart rate 84 beats/min, blood pressure 116/54 mm Hg, and respiratory rate 19 breaths/min (oxygen saturation 94% on room air). Additional findings included a grade 3/4 diastolic murmur heard at the right upper sternal border and weak pulses in both arms. There were no significant differences between blood pressures in the two arms and no other relevant findings.

The hemogram was normal, the erythrocyte sedimentation rate (ESR) was 2.0 mm/h (reference range, 0.0–15 mm/h), and C-reactive protein was 0.3 mg/dL (reference range, 0.0–0.3 mg/dL). Results of other laboratory tests were normal, including troponin I, plasma levels of electrolytes, renal function, albumin, thyroid-stimulating hormone, and antinuclear antibodies.

Electrocardiography showed normal sinus rhythm with left ventricular hypertrophy (Figure 1). Chest radiography demonstrated an increased cardiothoracic index with no further abnormalities (Figure 2).

Transthoracic echocardiography showed moderate left ventricular dilatation with normal systolic function (ejection fraction 66%; Video 1). The main finding was severe central AR explained by two different mechanisms: functional AR due to aortic root dilatation (3.8 cm, indexed 2.3 cm/m²) and direct aortic valve involvement with retraction of all three leaflets, most likely due to aortitis extension (Videos 2 and 3). Transesophageal echocardiography demonstrated diffuse wall thickening of the ascending, arch, and descending aortic segments (Video 4). Preoperative coronary angiography demonstrated an isolated 70% ostial LMCA stenosis (Video 5). Given the angiographic severity of the LMCA stenosis, no further assessment of this lesion (with either intravascular ultrasound or fractional flow reserve) was performed. Computed tomographic angiography of the aorta and neck vessels showed vascular damage in the major aortic branches, including bilateral carotid arteries, left subclavian artery, and ostial superior mesenteric artery stenosis (Figures 3 and 4).

This patient was taken urgently to the operating room. Because of severe vascular damage of the carotid arteries, during cardiopulmonary bypass, near-infrared spectroscopy was used to monitor cerebral oxygenation and for the detection of changes in cerebral blood flow that showed no abnormalities during procedure. Intraoperative findings included marked proximal aortic wall thickening and fibrotic changes (Figure 5) with almost complete LMCA occlusion. Proximal ascending aortic resection with a Dacron graft replacement, reconstruction of the LMCA by ostial amplification with autologous pericardium, and aortic valve replacement with a mechanical prosthesis (On-X, 23 mm) were performed without complications (Video 6). Histopathologic findings of the resected tubular ascending aorta demonstrated extensive fibrosis involving the intima, media, and adventitia, in addition to mononuclear cell aggregates, suggestive of a chronic and quiescent state of TA (Figure 6).

The patient had an uneventful postoperative course and was discharged 6 days after surgery. Four months after the procedure, she

VIDEO HIGHLIGHTS

Video 1: Transthoracic echocardiography showed moderate left ventricular dilatation (left ventricular end-diastolic volume 74 mL/m²) and preserved systolic function (ejection fraction 66%). *A2C*, Apical two-chamber; *A4C*, apical four-chamber; *PLAX*, parasternal long-axis; *PSAX*, parasternal short-axis.

Video 2: Transthoracic echocardiography, parasternal long-axis and parasternal short-axis zoomed aortic valve. In **(A)** and **(B)**, zoomed aortic valve showed cusp retraction, causing a triangular coaptation defect **(B)** with a severe central regurgitation jet visualized with color Doppler **(C, D)**. The aortic root at the sinuses of Valsalva was dilated, with a diameter of 3.8 cm (indexed 2.3 cm/m²).

Video 3: **(A)** Apical five-chamber view with color Doppler showing the severe aortic regurgitant jet. **(B)** AR continuous-wave Doppler shows a steep deceleration slope with a pressure half-time (PHT) of <200 msec. **(C)** Pulsed-wave (PW) Doppler with holodiastolic flow reversal in the abdominal aorta. **(D)** PW Doppler from the suprasternal view in the descending aorta with prominent holodiastolic flow reversal (*yellow arrowheads*). All parameters are compatible with severe AR.

Video 4: Transesophageal echocardiography. Midesophageal long-axis view with zoom, showing aortic cusp retraction with absent central coaptation **(A)**, leading to severe AR with color Doppler **(B)**. The descending aortic short-axis view **(C)** showed diffuse aortic wall thickening (4 mm in *red* measures); these thickened walls also were observed in the ascending portion and the aortic arch.

Video 5: Preoperative coronary angiography was performed, demonstrating an isolated 70% ostial left main coronary stenosis (*yellow arrows* in **A** and **C**, *red arrow* in the still frame **B**). **(D)** Right coronary artery without stenosis.

Video 6: Transthoracic echocardiography performed 3 days after surgery showed preserved biventricular systolic function and the mechanical aortic valve without abnormalities.

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remains asymptomatic with a good functional class and is currently treated with warfarin 2.5 mg/d, atorvastatin 40 mg/d, valproate 250 mg/d, and prednisolone 20 mg/d.

DISCUSSION

TA is a chronic, granulomatous, large-vessel vasculitis involving mainly the aorta and its main branches, with or without pulmonary artery extension.¹ TA affects mostly young women (75%–97% of cases), with an age of onset usually between 10 and 40 years. Although it is more frequent in Asia, TA can affect all races, and because of its relapsing and progressive course, ≥80% of patients will require long-term immunosuppression.²

TA's etiology is unknown, but several studies suggest a genetic predisposition of its immune-mediated process. Histopathologic findings

mainly denote extensive vessel granulomatous inflammation in the media and adventitia. During active inflammation, the media layer is affected by cytotoxic lymphocytes (especially gamma delta T lymphocytes), natural killer cells, macrophages, plasma cells, and giant cells.³ Inflammation evolves to fibrosis, and artery wall scarring leads to stenosis or occlusion, while elastic lamina and muscular media destruction can lead to aneurysm formation.⁴ Depending on the vascular lesion and the vessel involved, clinical manifestations may differ.

The clinical presentation is highly variable, being mostly subacute, which often leads to delay in diagnosis. Patients may present initially with nonspecific constitutional symptoms (weight loss, fatigue, low-grade fever) without any evidence of arterial occlusive disease (pre-pulseless stage); in advanced disease stages, patients can develop symptoms related to vascular occlusion, aneurysms, and stenosis (pulseless stage). Clinical manifestations of progressive arterial stenosis or dilatation include limb claudication or cyanosis, lightheadedness, neck tenderness related to carotidynia (carotid artery tenderness), diminished peripheral pulses (frequently in radial arteries), murmurs in stenotic territories, or AR signs on physical examination in patients with aortic root and ascending aortic dilatation.⁵ Discrepant blood pressure (>10 mm Hg difference) between arms is typically present, whereas angina pectoris may be related to LMCA narrowing in addition to myocardial infarction or even sudden death.

Coronary artery stenosis occurs in about 9% to 11% of patients with TA, usually affecting the ostial segments (73% of cases) because of the direct extension of aortic wall inflammation while sparing the distal coronary portions.⁶ Angina and DOE may occur because of coronary stenosis in addition to heart failure symptoms associated with AR or pulmonary hypertension. When present, coronary lesions can be further assessed with functional tests (such as fractional flow reserve) for determining the hemodynamic impact and the need for revascularization. AR in patients with TA may be either functional because of aortic dilatation or aneurysm or caused by direct valve involvement with foreshortening or leaflet(s) retraction because of aortitis extension.

Physical examination for the detection of arterial lesions has low sensitivity (14%–50%) but good specificity (71%–98%) compared with angiography. It should focus on accurate blood pressure measurement, pulse palpation, bruit identification, and careful cardiac auscultation.⁷

There are no gold-standard imaging or laboratory tests for TA diagnosis. Initial nonspecific constitutional symptoms may delay TA diagnosis until the onset of vascular complications. Laboratory abnormalities are nonspecific and usually reflect only an inflammatory process. Elevations in acute phase reactants, such as C-reactive protein or ESR, may be present but are not reliable indicators of disease activity because they can be normal even in the setting of active disease.⁸

Imaging studies are indicated mainly for assessing narrowing of the aorta (or its primary branches), including catheter-based angiography, computed tomographic angiography, magnetic resonance angiography, ¹⁸F-fluorodeoxyglucose positron emission tomography, duplex ultrasound, and echocardiography. They are essential for establishing the primary diagnosis and for determining the extent of vascular damage. None of these modalities are specific for the evaluation of disease activity.¹ TA arterial lesions are usually circumferential areas of luminal narrowing typically related to the origin of the principal branches of the aorta. The inflammation may be localized to a portion of the thoracic or abdominal aorta but also may involve the entire vessel. The initial vascular lesions appear mostly in the left subclavian artery,

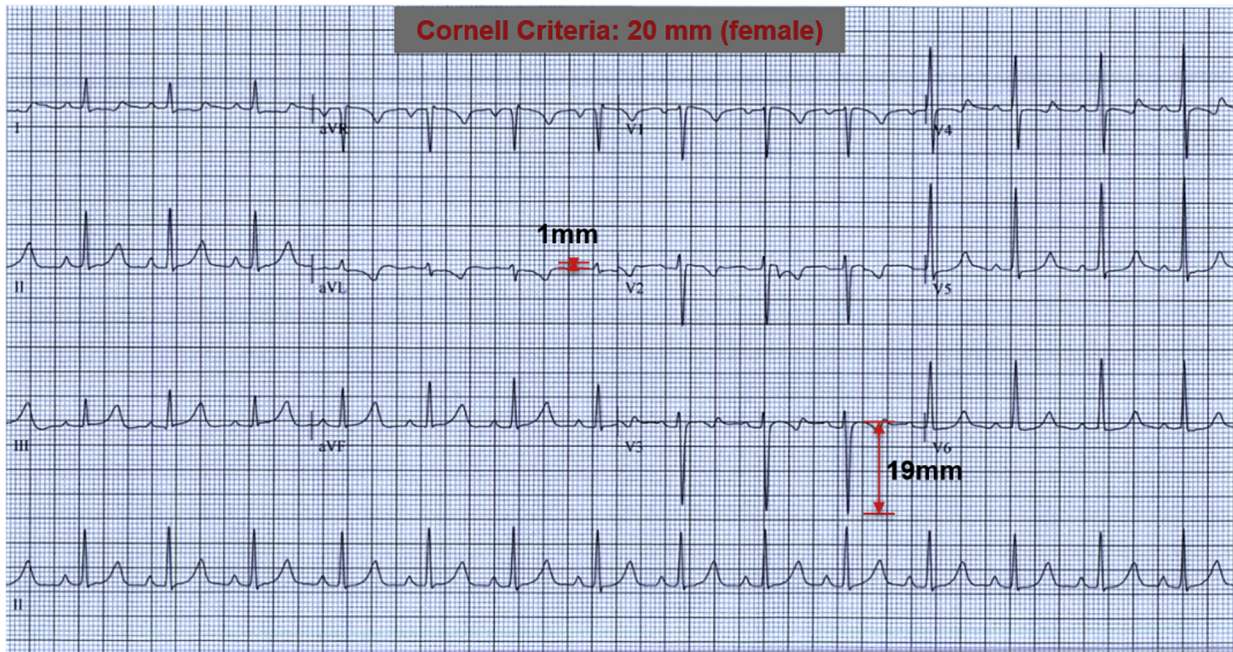


Figure 1 Electrocardiography showed normal sinus rhythm with left ventricular hypertrophy by Cornell voltage criteria.

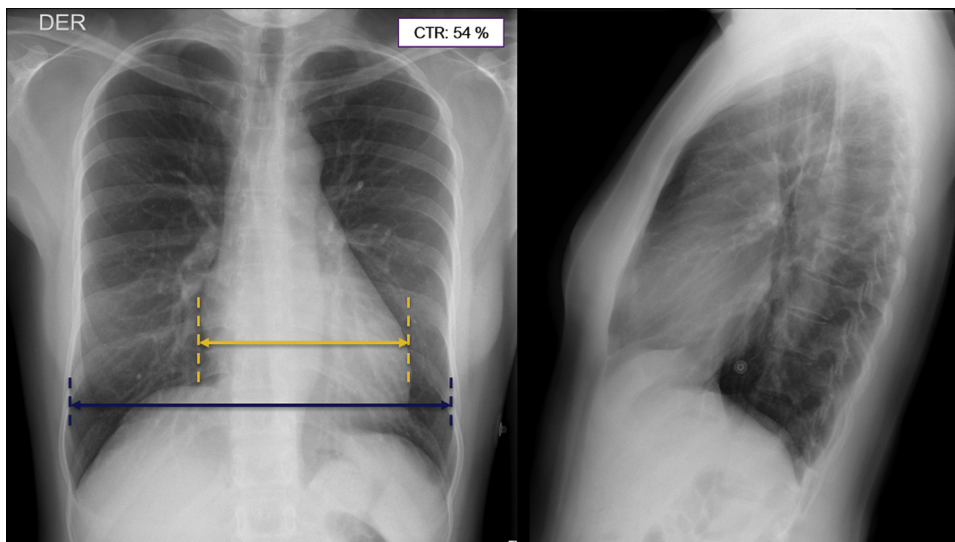


Figure 2 Chest radiography with a cardiothoracic ratio (CTR) of 54%, suggestive of cardiomegaly. No widened mediastinum was observed.

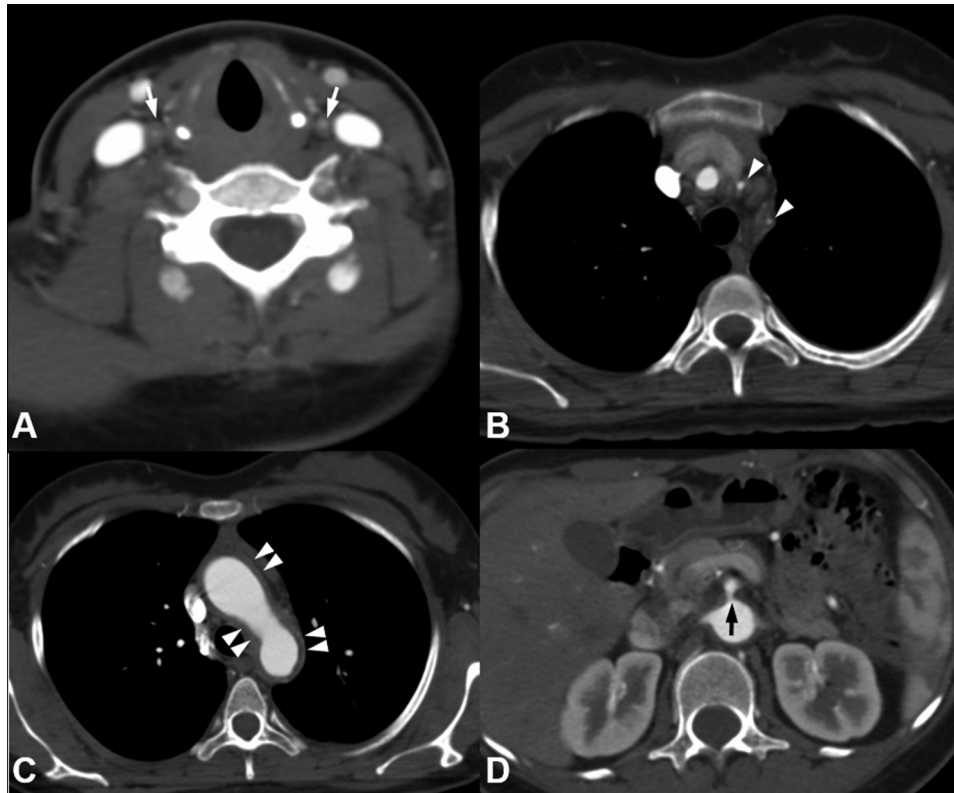


Figure 3 Main vascular findings on computed tomography. Severe stenosis in the cervical segments of both common carotid arteries is seen (*white arrows in A*) with diffuse thickening of the arterial wall and severe stenosis in the origin of the left common carotid and left subclavian artery (*white arrowheads in B*). This marked thickening was also seen in the thoracic (*double arrowheads in C*) and abdominal aorta, with ostial stenosis of the superior mesenteric artery (*black arrow in D*).

progressing to the left common carotid, vertebral, brachiocephalic, right subclavian artery, right carotid, and the rest of the aorta. The pulmonary artery is involved in up to 50% of cases. Magnetic resonance angiography and computed tomographic angiography (even for coronary arteries) are the best noninvasive studies for imaging the arterial tree and determining vascular lesions.

On the basis of the Numanó's angiographic classification of TA involvement, our patient was classified as IIb (vascular lesions in the ascending aorta, aortic arch with its branches, descending thoracic aorta, and less compromise of abdominal aorta).⁹ TA and giant cell arteritis are similar in terms of aortitis compromise and histologic features; however, patients with giant cell arteritis are usually >50 years of age, and it mainly affects branches of the external carotid artery.

Arterial complications and a progressive course are the two major determinants of long-term prognosis.¹⁰ The 15-year survival rate of patients with TA without arterial complications or a progressive course is near 95%.¹⁰ However, when major complications occur, 15-year survival decreases to 66%. Up to 50% of these patients will relapse and experience vascular complications within 10 years of the initial diagnosis. C-reactive protein and carotidynia are associated with relapses, whereas retinopathy, thoracic wall involvement, and a progressive clinical course are related to the onset of vascular complications.²

There are no validated disease activity criteria for TA. Activity disease could be defined as a combination of clinical signs or symptoms

of vascular ischemia or inflammation, increased ESR, imaging features, and systemic symptoms not attributable to another disease.⁸ When surgically removed, arterial tissue samples are available for histopathologic study, and definite diagnosis may be established in addition to disease status (active inflammation vs quiescent scar) for treatment purposes.

Early initiation of corticosteroids is the mainstay of treatment. Up to 50% of patients are not able to maintain sustained remission with glucocorticoid therapy alone. Therefore, disease-modifying antirheumatic drugs such as methotrexate, mycophenolate mofetil, or azathioprine and cytotoxic drugs (such as cyclophosphamide) may be necessary. Patients unable to achieve remission with disease-modifying antirheumatic drugs are treated with biologic agents such as infliximab, etanercept, adalimumab, tocilizumab, and rituximab.¹¹

In the chronic and pulseless stage of TA, revascularization of severely stenotic lesions may be required, which can be done percutaneously or surgically. Although percutaneous angioplasty with or without stent has good short-term success (81%–100%), the restenosis rate is as high as 71.4% over 1.3 years.^{12,13}

Surgical revascularization is superior to percutaneous treatment for long-segment stenosis, but results are inferior compared with patients with atherosclerotic disease. TA vascular lesions are longer, with a larger fibrotic burden and with persistent inflammation despite quiescent clinical or laboratory status. About 20% of



Figure 4 Major aortic branch stenosis. Oblique reformatting, maximum intensity projection. Severe stenosis is seen in the left common carotid (*black arrow*) with thickening of the arterial wall. The left subclavian artery shows proximal stenosis and is occluded proximal to the origin of the left vertebral artery (*white arrow*).

patients with TA will require surgical treatment for vascular complications, primarily stenotic lesions.⁷ In patients with artery bypass surgery, occlusion or restenosis occurs in up to 31% over 3 to 6 years.¹² Coronary artery bypass grafting must avoid using the internal mammary artery because of the high prevalence of subclavian artery stenosis. There is a lack of data regarding other arterial conduits, but given the pathophysiology of the disease, higher patency with saphenous vein grafts is expected. Some authors have proposed the interposition of pericardium tissue or Dacron between a saphenous vein graft and the aortic wall.⁶ When planning these procedures, careful evaluation of the extent of arterial disease in the aorta and its main branches is critical for ensuring and monitoring proper brain perfusion during cardiopulmonary bypass (as performed in our case).

Revascularization must be done when the disease is not active, because patients with active inflammation at the time of surgery have a higher 5-year risk for arterial complications or restenosis.¹⁴ Patients with active disease, on and off steroids at the time of surgery are more likely to require new intervention (within 5–10 years) compared with those with quiescent status irrespective of steroid

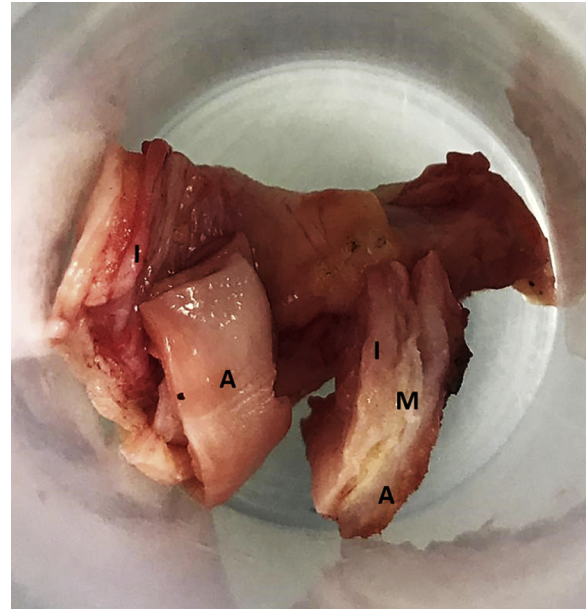


Figure 5 Gross photograph of the ascending aorta. Notice the significant intimal thickening with attenuation of the media and adventitial fibrosis (the major cause of the aortic wall thickening). A, Adventitia; I, intima; M, media.

use.¹⁵ Better long-term results are obtained when patients are on immunosuppressive therapy with a normal ESR (stable stage disease), similar to our case.

CONCLUSION

LMCA stenosis with concomitant severe AR is unusual in young patients. This presentation may occur in patients with TA due to local extension of aortitis into the aortic valve leaflets and also into the ostial coronary arteries. Surgical management for coronary artery revascularization and severe valvular regurgitation are the main treatment for patients with TA with such abnormalities. Surgical timing is crucial, ideally while patients do not have active disease. Ideal conduits for coronary artery bypass grafting are pericardial patches and saphenous vein grafts, which are preferred because of their longer patency and the high likelihood of subclavian artery stenosis. Concomitant systemic treatment with anti-inflammatory drugs is critical to prevent symptomatic recurrence and to delay disease progression.

Chest pain and DOE in patients with TA should be taken seriously, and early cardiology consultation is advised to rule out severe coronary artery disease and severe AR.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.case.2020.09.004>.

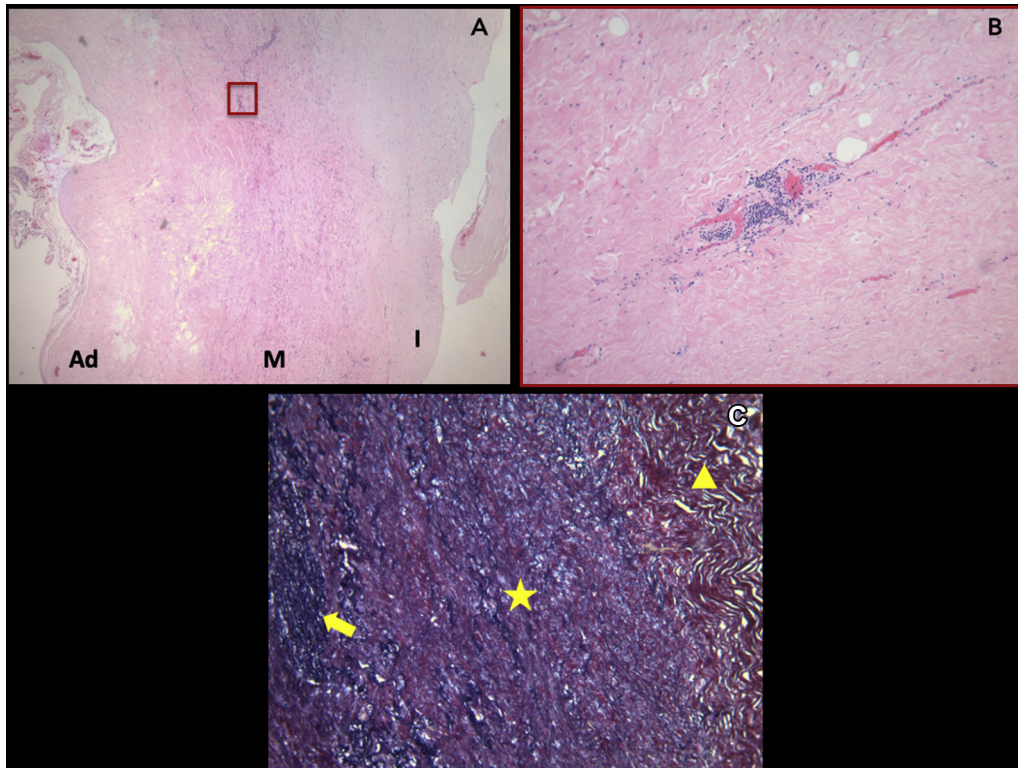


Figure 6 Histopathologic findings of the resected ascending aorta. **(A)** Aortic wall (hematoxylin and eosin, 4 \times): the typical architecture of the aortic wall was lost, with extensive fibrosis involving intima (I), media (M), and adventitia (Ad). **(B)** Focus on the aortic media (*red square* on hematoxylin and eosin, 10 \times): inflammatory foci with mononuclear cell aggregates composed mainly of lymphocytes and plasma cells. Given the chronic and quiescent status of the disease, no giant cells were observed. **(C)** Focus on the aortic media (van Gieson's stain, 10 \times): this special stain was performed to assess elastic fibers. Note the limited presence of elastic fibers in the media (*yellow arrow*), being extensively replaced by fibrosis (*yellow star*). There is also fibrosis extension into the intimal layer (*yellow arrowhead*).

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