

## Chronic angina secondary to Takayasu arteritis. Report of one case

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### ABSTRACT

*Chronic coronary syndromes are usually considered uncommon in young women, related to slower progression of atherosclerotic coronary artery disease, have atypical clinical presentations, and experience less diagnostic investigation. Non-atherosclerotic causes of coronary artery disease should be considered in young women experiencing angina. We report a 25-year-old woman who consulted for five months of moderate exertion angina. Physical examination revealed a right carotid bruit and asymmetrical upper extremity peripheral pulses. Initial work-up and imaging allowed to diagnose aortitis with bilateral coronary ostial stenosis secondary to Takayasu's arteritis. The patient experienced an apparent clinical response to initial medical therapy. However, follow-up evaluation revealed persistence of significant ischemia and requirement for myocardial revascularization. A percutaneous coronary intervention was performed.*

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**Key words:** Aortitis; Coronary Stenosis; Myocardial Revascularization; Takayasu arteritis.

## Síndrome coronario crónico secundario a aortitis y enfermedad coronaria ostial bilateral. Informe de un caso

*Los síndromes coronarios crónicos son infrecuentes en mujeres jóvenes, quienes suelen presentar una lenta progresión de enfermedad coronaria aterosclerótica, tienen presentación clínica atípica y son menos sujetas a exploración diagnóstica. Se deben considerar causas no ateroscleróticas de enfermedad coronaria en mujeres jóvenes con angina. Informamos una paciente de 25 años que consultó por cinco meses de angina con esfuerzos moderados. Al examen físico presentaba un soplo carotídeo derecho y pulsos asimétricos de extremidades superiores. La exploración de laboratorio inicial y posterior evaluación multimodal permitió evidenciar la presencia de aortitis y estenosis de ambos ostium coronarios, concordante con el diagnóstico de una arteritis de Takayasu. Inició terapia médica con respuesta clínica aparentemente favorable. No obstante, la evaluación cardiológica no invasiva en el seguimiento permitió corroborar la persistencia de isquemia significativa y necesidad de revascularización miocárdica. Se realizó una intervención coronaria percutánea de ambos ostium, con una evolución favorable.*

**Palabras clave:** Aortitis; Arteritis de Takayasu; Estenosis Coronaria; Revascularización Miocárdica.

**T**akayasu arteritis (TAK) is a chronic inflammatory disease which involves large-caliber vessels, including the aorta and its major branches. TAK has an annual incidence rate of 0.4-3.4 per million people, primarily affecting patients under 50 years of age, with female predominance (70-97%)<sup>1,2</sup>. Clinical presentation may include a constitutional or “pre-pulseless” phase characterized by fever, weight loss, fatigue and occasionally vascular inflammatory signs such as tenderness or pain over arteries named carotidynia and a fibrotic or “pulseless” phase entailing symptoms secondary to arterial stenosis as stroke and myocardial infarction<sup>3,4</sup>. Diagnostic criteria are mostly based on symptoms, physical examination, imaging findings and non-specific inflammatory markers<sup>1,5</sup>. Delayed diagnosis is common. Overall morbidity is dependent on ethnicity, response to medical therapy, and severity and extent of vascular sequelae<sup>1,5,6</sup>.

We present a case of chronic coronary syndrome (CCS) in a young woman secondary to TAK, reviewing important considerations in the assessment and treatment of this condition.

### Case Presentation

A 25-year-old woman was referred to our institution because of five months of retrosternal, oppressive chest pain triggered by moderate exertion (CCS II). Pain had an approximate duration of three minutes and relieved by rest. It associated with dyspnea (NYHA II) and palpitations. She had completed long-term penicillin treatment for latent syphilis discovered during a pregnancy screening seven years before. She used oral contraceptives. The patient denied taking other medication and reported no smoking or illicit drug consumption. The patient presented with normal vital signs. Physical examination exposed right carotid artery bruit and peripheral pulse asymmetry between upper extremities, with no other remarkable alterations. Initial work-up included:

#### Laboratory

Hemoglobin 11.5 g/dl, leukocytes 7400/ml, platelets 477000/ml; erythrocyte sedimentation rate (ESR) was 70 mmHg (normal value < 20 mm/h); creatinine 0.61 mg/dl; total cholesterol 158 mg/dl; HDL cholesterol 52 mg/dl; LDL cholesterol 90 mg/dl; triglycerides 98 mg/dl.

#### Electrocardiogram (ECG)

Sinus rhythm, nonspecific ST depression in V4-V5 (Figure 1A).

#### Chest X-ray

Normal.

#### Echocardiography

Left ventricle had normal dimensions, global and regional systolic function was normal, ejection fraction was 60%. Diastolic function was normal. Right chambers had normal dimensions; right ventricular function was normal. Aortic, mitral, and tricuspid valves had trivial regurgitations. Aortic root and ascending aortic walls were thickened (Figure 2A-B). Left and right coronary artery ostial stenosis could be observed (Figure 2C).

#### Exercise ECG

Exercise stopped due to worsening angina and ST elevation in aVR with co-existent multi-lead ST depression at 5:12 minutes of Bruce Protocol (Figure 1B), achieving 72% of maximal heart rate. No arrhythmias were observed. Symptoms and ECG abnormalities relieved during recovery.

Complimentary non-invasive imaging was requested:

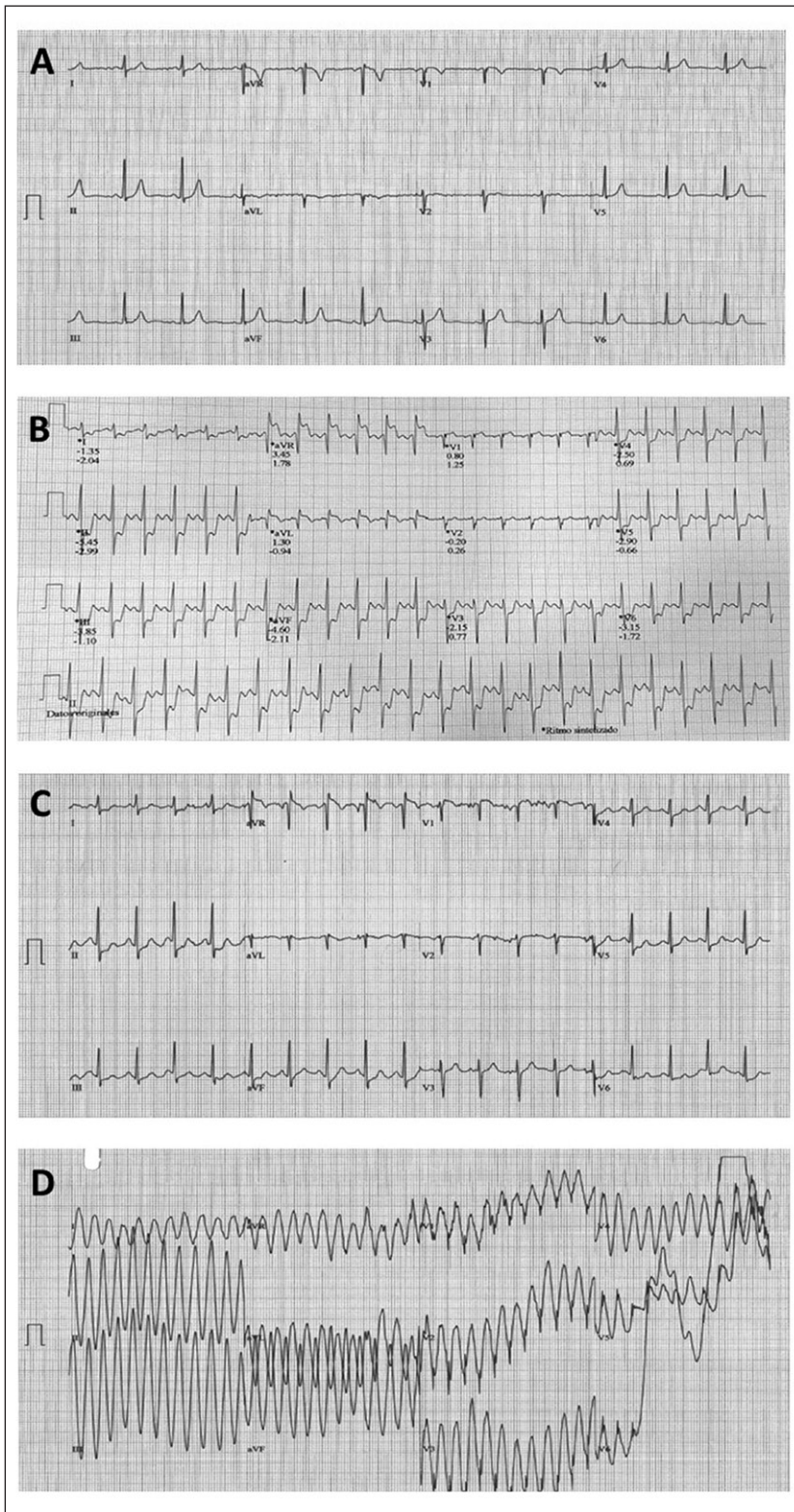
#### Coronary computed tomography (CCT)

Increased circumferential wall thickness of aortic root, sinotubular junction and ascending aorta (Figure 2D). Significant stenosis of left main coronary artery and right coronary artery ostia was observed (Figure 2E).

#### Positron emission tomography-computed tomography (PET-CT)

Increased 18F-FDG uptake with maximal SUV 4.0 in the aortic root and ascending aorta (Figure 2F).

The patient was admitted to the medical ward under presumption of inflammatory aortitis secondary to large vessel vasculitis for completing study. Further laboratory included: antinuclear antibody negative, anticardiolipin antibody negative, B2-glycoprotein I negative, extractable nuclear antigen antibodies panel negative; treponemal test (MHA-TP) reactive; non-treponemal test (VDRL) non-reactive; HIV negative. TAK was diagnosed according to American College of Rheumatology criteria, with an active status con-



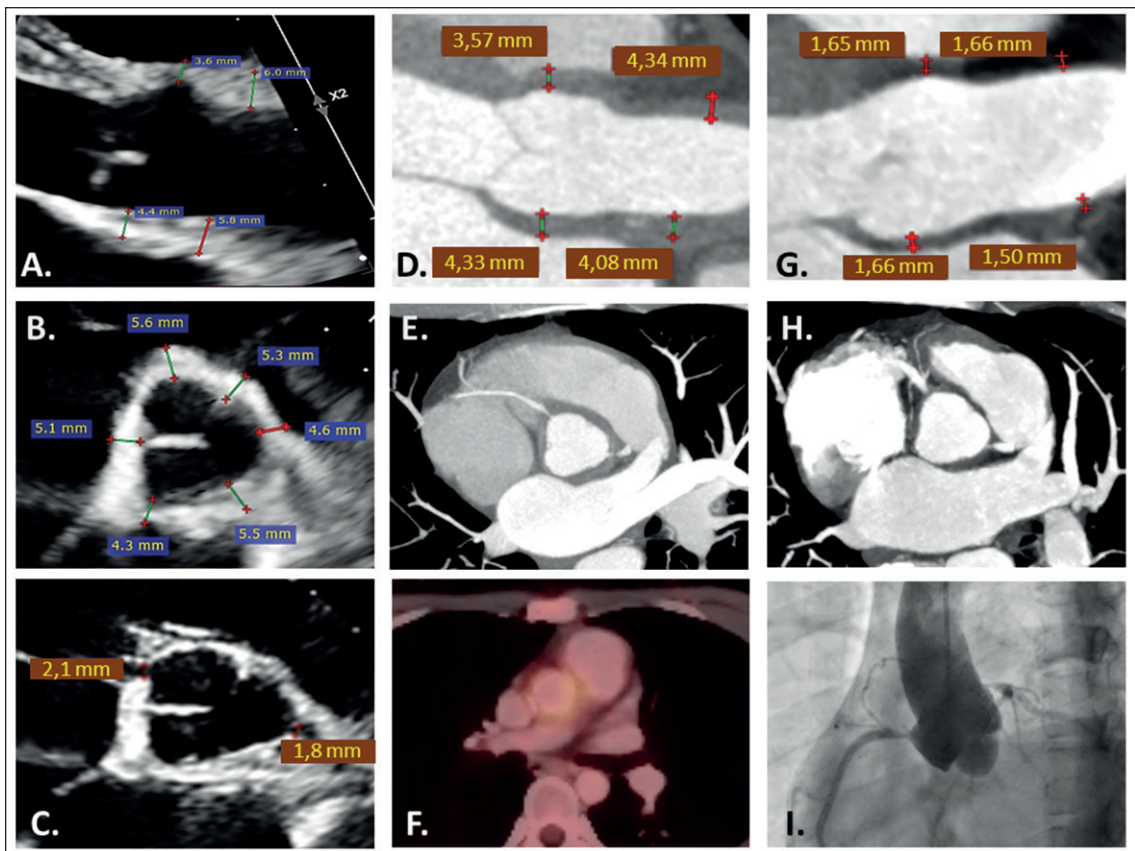
**Figure 1.** Electrocardiographic assessment at baseline and follow-up. **A)** Baseline resting ECG showing normal sinus rhythm, non-specific repolarization abnormalities. **B)** Baseline exercise ECG at second stage of Bruce Protocol, showing ST segment elevation at aVR and diffuse horizontal/downsloping ST depression. **C)** Follow-up exercise ECG at first stage of Bruce Protocol showing upsloping ST segment depression. **D)** Follow-up exercise ECG at second stage of Bruce Protocol showing ventricular tachycardia.

sidering Indian Takayasu Clinical Activity Score of 6 points. She was prescribed prednisone 1 mg/Kg daily (60 mg) and azathioprine 100 mg daily as immunosuppressive therapy. Bisoprolol 2.5 mg, acetylsalicylic acid 100 mg and atorvastatin 40 mg daily for management of CCS.

At 3-months of follow-up the patient referred a decrease in angina frequency and severity. C-reactive protein (CRP) was 0.2 mg/dl (normal range < 5 mg/dl), and ESR was 6 mm/h. Exercise ECG with Bruce protocol was performed to assess treatment response; the patient experienced early and progressive angina, discrete ST elevation in aVR with co-existent multi-lead ascending ST (Figure 1C), and cardiac arrest at 4:32 minutes of

exercise (Figure 1D). She recovered spontaneous circulation after one cycle of chest compressions and was admitted to intensive care for monitorization, maintaining hemodynamic stability and sinus rhythm. Coronary CT showed normal aortic parietal width (Figure 2G), severe stenosis of left main and right coronary artery ostia (Figure 2H), and no other coronary lesions were observed.

Discussed at our Heart Team, percutaneous coronary intervention (PCI) was planned as myocardial revascularization strategy. Cineangiography corroborated left main coronary artery ostia stenosis and right coronary artery stenosis (Figure 2I). PCI using drug eluting stents were performed in left main coronary artery ostia and



**Figure 2.** Multimodality imaging assessment at baseline and follow-up. **A-B)** Baseline echocardiography. Paraesternal long and short axis views zoom showing parietal thickening of the aortic wall at root and ascending aorta between 3.6-6.0 mm (normal value in women  $1.8 \pm 0.7 \text{ mm}^{20}$ ). **C)** Baseline echocardiography. Paraesternal short axis view with zoom showing bilateral coronary ostia stenoses. **D)** Baseline cardiac CT showing wall thickening at aortic root and ascending aorta between 3.57-4.34 mm (normal value  $0.8 \pm 0.7 \text{ mm}^{20}$ ). **E)** Baseline cardiac CT (MPI) showing diffuse aortic root parietal thickening and bilateral coronary ostia stenoses. **F)** Baseline PET-CT showing increased 18F-FDG uptake at ascending aorta. **G)** Follow-up cardiac CT showing reduction of aortic root and ascending aorta parietal width near normal limits. **H)** Follow-up cardiac CT (MPI) showing persistence of ostial coronary stenoses. **I)** Aortography showing bilateral ostial coronary stenoses.

right coronary artery ostia, without complications. The patient was discharged after 3 days of monitoring, asymptomatic and with good response to rehabilitation. At 6 months after PCI, the patient remained asymptomatic.

## Discussion

This report describes the case of a young woman with CCS secondary to TAK. To the best of our knowledge, no data regarding prevalence of TAK in young women with CCS has been published. A retrospective series of women < 40 years presenting at an emergency department for acute ischemic heart disease, reported a 10% prevalence of TAK<sup>7</sup>. TAK typically affects young women between 20 and 40 years, mostly considered at low-risk for atherosclerotic coronary artery disease. Coronary artery involvement has been described in 5-30% of TAK patients, mostly as ostial stenosis associated to aortitis<sup>8,9</sup>. Diffuse or focal coronary arteritis, enhanced atherosclerotic coronary artery disease and coronary aneurisms have also been described<sup>8,9</sup>. Coronary artery involvement is associated with poor long-term prognosis<sup>6</sup>.

This case reflects the importance of systematically studying young patients with angina. The pre-test probability of obstructive coronary artery disease considering age, sex and type of angina was 5% for our patients<sup>10</sup>. Current CCS guidelines suggest an initial work-up prior to assessment of pre-test probability, allowing to identify modifiers of clinical likelihood for coronary artery disease. In our patient, non-specific repolarization abnormalities in electrocardiogram and aortic wall thickening at echocardiography increased the clinical likelihood for coronary artery disease and aortic disease respectively. Exercise ECG documented angina with high-risk features, despite medical treatment and patient-reported improvement at follow-up, defining the need for myocardial revascularization.

Multimodality cardiovascular imaging, including CCT and PET-CT are crucial for diagnosis and follow-up of TAK. CCT is a reliable alternative to coronary angiography, with reported sensitivity of 95% and specificity of 100% for diagnosis of stenosis of the aorta or branches at end-stage disease<sup>3,5</sup>. CCT has limited capacity to characterize mural inflammation in early stages, nonetheless, "double ring" appearance on post-

contrast images, determined by brightly enhanced outer ring of inflamed media and adventitia surrounding poorly enhanced edematous intima has been described as an early finding of TAK<sup>3</sup>. PET-CT has been suggested as biomarker for diagnosis of TAK, with reported sensitivity 70-73% and specificity 77-84%<sup>5</sup>. PET-CT also has been proposed as disease activity marker, superior to ESR and CRP in the assessment of response to therapy<sup>3</sup>. During clinical remission, higher PET Vascular Activity scores have been reported as predictors of clinical relapse<sup>11</sup>. In our patient, CCT allowed to confirm presence of aortic wall thickening and coronary artery ostial stenosis at baseline, persistence of significant coronary ostial stenosis despite reduction of aortic width and normalization of inflammatory markers; and helped to discard other coronary lesions and left subclavian artery stenosis. PET-CT was useful at diagnosis in our patient, albeit costs limited its usage upon follow-up.

Management of CCS in TAK patients presents several challenges. Current guidelines suggest medical therapy and indications for revascularization for coronary stenosis in TAK are alike patients with atherosclerotic coronary artery disease<sup>12</sup>. Retrospective studies described no differences in cardiovascular mortality of TAK patients undergoing myocardial revascularization versus medical treatment, despite most patients presenting ostial coronary artery stenosis<sup>13,14</sup>. Immunosuppressive regimens based on corticosteroids and azathioprine have reported at least a partial clinical response in 84% of patients, achieving angiographic stabilization, although with no regression of significant stenosis<sup>15</sup>. Clinical studies with tocilizumab, an IL-6 receptor antibody, suggest stabilization or regression of stenosis in 71-86% of treated patients<sup>16,17</sup>. Retrospective cohort studies comparing coronary artery bypass graft (CABG) versus PCI have described similar cardiovascular mortality, albeit PCI have been associated with higher restenosis rates<sup>13,14,18,19</sup>. Due to the high frequency subclavian artery stenosis in TAK patients, limiting internal mammary artery blood flow, CABG with saphenous vein graft is more frequently performed despite their higher tendency of graft failure at follow-up<sup>8,14</sup>. Most studies compare CABG against PCI with bare-metal stents, demanding a need for long-term efficacy results with contemporary drug-eluting stents<sup>13,14,18,19</sup>.

Revascularization during active phase of TAK has been associated to higher rates of graft failure or restenosis<sup>14</sup>. Our patient experienced significant ischemia despite medical treatment, therefore candidate to coronary revascularization and thus discussed at the Heart Team. Considering our patient was young, with no other indication for cardiac surgery, but with potential requirement for future interventions associated to TAK recurrence or aging, our Heart team agreed PCI with surgical back-up offered a better alternative as first revascularization approach.

**Statement of consent:** Authors confirm that written consent for submission and publication of this case report, including images, was obtained from the patient in line with COPE guidance.

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