

Diagnostic dilemmas in a case of early-onset large vessel vasculitis

Andra Carmina Ciotoracu¹, Doina Ramba¹, Luiza Pana¹, Razvan Adrian Ionescu^{1,2}

¹3rd Internal Medicine Department, Colentina Clinical Hospital, Bucharest, Romania

²"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

ABSTRACT

Vasculitides are inflammatory disorders which affect the blood vessels. There are three major categories of vasculitides depending on the size of the injured vessels. Although each category can affect any size artery, usually large vessel vasculitis affects large arteries. Takayasu arteritis and Giant Cell arteritis are known to be the two main types of large vessel arteritis. We present the case of a patient with a delayed diagnosis of Takayasu disease who sequentially develops a series of complications. The atypical evolution of the disease confirms once again the complexity of the vasculitic disorders and raises questions about the understanding of their pathophysiological mechanisms.

Keywords: Takayasu, early onset, large vessel vasculitides

INTRODUCTION

Large vessel vasculitis is characterized by chronic granulomatous inflammation predominantly affecting the aorta and its major branches. We distinguish two categories of large vessel vasculitis: Takayasu arteritis, also called "pulseless disease" and Giant Cell Arteritis (GCA), also called "temporal arteritis", both sharing common pathogenic pathways. Histologically, all three layers of the vessels are affected, leading to stenotic or aneurysmal lesions and thrombus formation (1,2).

Takayasu arteritis was first described by a Japanese ophthalmologist in 1905 regarding the case of a 21 year old woman after examining her eyegrounds. Although Dr. Takayasu is recognized as being the one who first reported this disease, there are prior case reports dating from 1761, 1830 and 1956 that may refer to Takayasu arteritis (3,4).

Diagnostic criteria for Takayasu arteritis were first proposed in 1988 by Ishikawa and consisted of one mandatory criterion, two major criteria and 9 minor criteria. The obligatory criterion was the age of onset ≤ 40 years. In 1990, the American College of Rheumatology (ACR) published the classification criteria for Takayasu arteritis, having as purpose an

easier identification of the patients to be evaluated in studies. The age of onset was still between the criteria of classification until 1995, when Sharma et al. proposed some modifications on Ishikawa diagnostic criteria. Modified Ishikawa criteria had better sensitivity and specificity for identifying Takayasu arteritis. Regarding early-onset Takayasu, in 2008 EULAR/PRINTO/PRES criteria have been validated to be used in patients younger than 18 years (Table 1) (4,5).

Presently, further efforts are made to develop a validated set of diagnostic criteria and a single classification system for the primary systemic vasculitides and to update the existing classification criteria through The Diagnostic and Classification Criteria in Vasculitis Study (4).

Giant Cell Arteritis and Takayasu arteritis are differentiated from one another based on the age of onset, symptoms, vascular distribution and epidemiologic aspects. The pathogenesis of these vasculitides is not fully understood, but they share similarities. There are different clinical subtypes of GCA, one of them being Large-Vessel Giant Cell Arteritis (LV-GCA). This subtype is hard to differentiate from Takayasu arteritis, but they may differentiate by the

TABLE 1. Takayasu's arteritis criteria established by European League Against Rheumatism/Pediatric Rheumatology International Trials Organization/Pediatric Rheumatology European Society (2008) (6)

Mandatory criteria	
Angiographic abnormality	Angiography (conventional, CT, and MRI) of the aorta, its main branches or pulmonary arteries showing aneurysm/dilatation, narrowing, occlusion, or thickened arterial wall, not due to any other causes
Additional criteria (plus one of the five following criteria)	
(1) Pulse deficit or claudication	Lost/decreased/unequal peripheral artery pulse Symptoms of claudication: Focal muscle pain induced by physical activity
(2) Blood pressure discrepancy	Discrepancy of four limb systolic blood pressure >10 mmHg in any limb
(3) Bruits	Audible murmurs or palpable thrills over large arteries
(4) Hypertension	Systolic/diastolic blood pressure > 95th centile for height
(1) Acute phase reactant	Erythrocyte sedimentation rate > 20 mm per hour or C-reactive protein above normal

type of aortic involvement. Further studies are needed, in order to fully understand and to define the large spectrum of vasculitides (7,8).

CASE REPORT

We present the case of a 41 years old female patient, nonsmoker, diagnosed with Takayasu arteritis approximately 16 years ago and recently admitted to our hospital for reevaluation of the disease and treatment optimization. She is now complaining of inflammatory pain and stiffness of the shoulder and hip girdle, bilateral leg claudication and intermittent diffuse headache. Biologically, inflammatory syndrome with an erythrocyte sedimentation rate of 53 mm/h is present. She also has a medical history of stage 2 arterial hypertension, hyperthyroidism and exogenous Cushing's syndrome.

The onset of rheumatic disease was in 1988, when the patient was 11 years old, with dull, persistent cervicalgia and pain, weakness and numbness of both arms. No history of tuberculosis infection in the family or any other particular disease. A minor right bundle branch was found on the EKG. The clinical examination revealed kyphoscoliosis, paresthesia of the right upper limb and extrapyramidal syndrome with suspended sensory loss at the T3-T7 level. The diagnostic of syringomyelia was suspected and CT scan was recommended. One year later, she was admitted again at the hospital, with the persistency of

the symptoms. We note the erythrocyte sedimentation rate of 42 mm/h and the pituitary fossa that appears smaller than normal. Arnold-Chiari malformation is suspected, further investigation being needed.

No other medical investigations were done until October 2003, at the age of 26, when the woman was admitted at the hospital experiencing fatigability, paresthesia of the extremities and Raynaud phenomena. Physical examination on this admission found the absence of left radial pulse, arterial blood pressure in the right arm of 120/50 mmHg, compared to 80/50 mmHg in the left arm, apical systolic murmur with radiation to the axilla, bilateral carotid bruits and periumbilical bruits. Laboratory tests revealed inflammatory syndrome (CRP level of 22 mg/l, ESR 80 mm/h, fibrinogen level of 6,47 g/l), the absence of antinuclear antibodies, rheumatoid factor and cryoglobulins. VDRL and hepatitis tests were found negative. EKG showed minor right bundle branch and echocardiography showed minimal tricuspid and mitral regurgitation, with no haemodynamic significance. Chest X-ray was normal. An angiography, recommended by the cardiologist, was performed and found multiple large-vessel stenosis. The clinical and imagistic data were consistent with Takayasu arteritis diagnosis. Therapy with Prednisone (60 mg/day, with subsequent decrease of corticosteroid doses), calcium blocker (Felodipine 10 mg/day), pentoxifylline (800 mg/day) and antiplatelets (aspirin 75 mg/day) was initiated.

In the following year, two left subclavian stenting procedures were performed but without success. In 2005 and in 2007 the angiography was repeated, revealing a right common carotid artery with 40-50% stenosis, a left carotid artery with 60-70% stenosis, 50-60% stenosis of right subclavian artery, 70-80% stenosis of the left subclavian artery before the vertebral artery origin and complete obstruction above vertebral artery origin. Abdominal aorta was also affected by the disease with 30-40% stenosis above renal arteries origins. Iliac arteries had no significant lesions.

In 2008 (Fig. 1), 2013 and 2017 CT angiography was used to assess disease progression. The one from 2013 revealed a 50-60% superior mesenteric artery stenosis and a 80-90% stenosis of the left internal mammary artery.

During these years, the patient continued the treatment with corticosteroids (Prednisone and Metilprednisolone pulse therapy), calcium blocker, antiplatelet drug and hydroxychloroquine (200 mg/

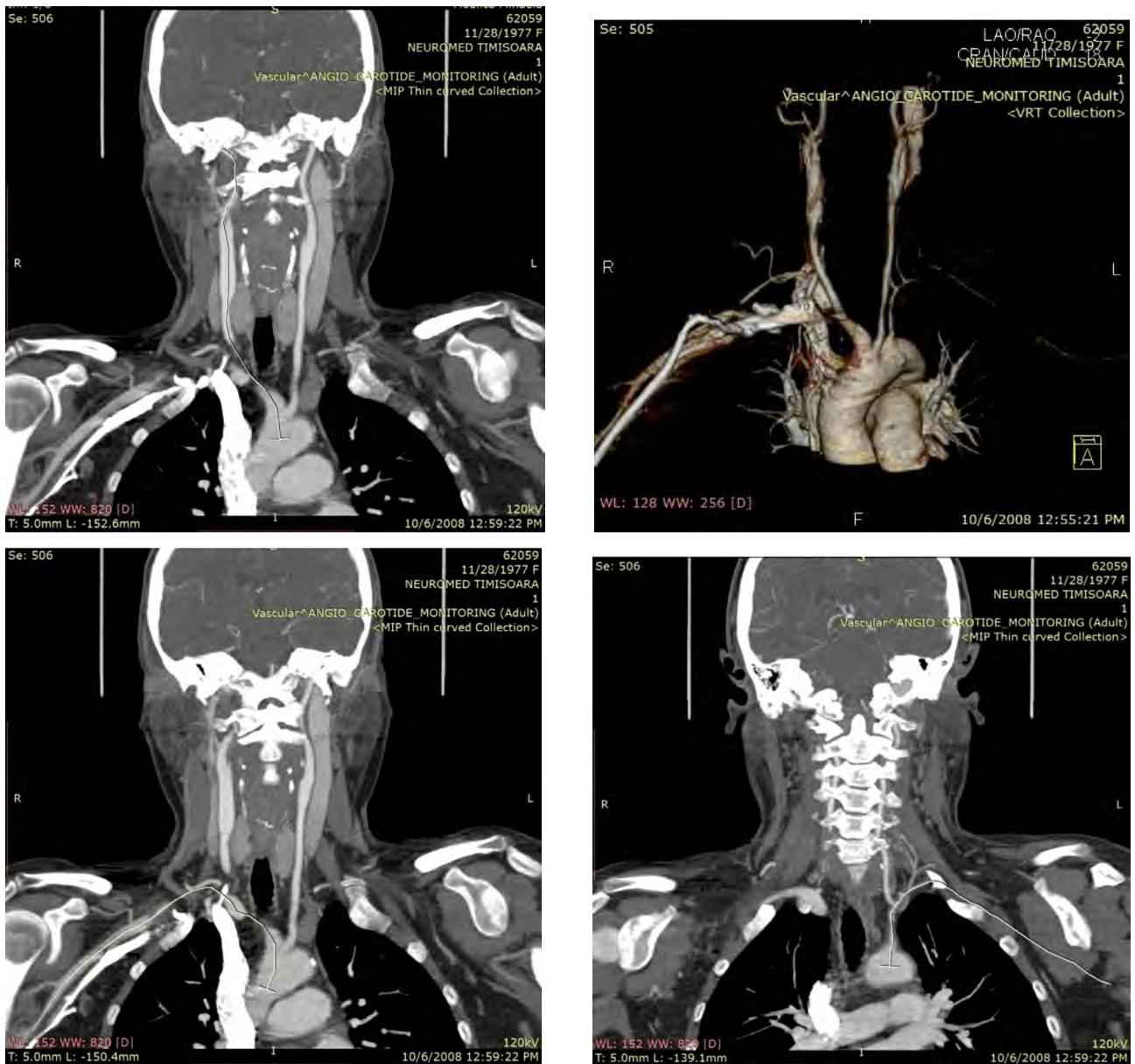


FIGURE 1. Computed Tomography Angiography (2008) revealing bilateral stenosis of carotid and subclavian arteries

day). Considering the persistency of the symptoms, in 2012 it was decided to initiate azathioprine therapy (50 mg/day). Due to progression of the disease, in 2013 the azathioprine dose has been increased (100 mg/day).

In 2011, the patient accuses worsening of the symptoms with left hemi thoracic pain, irradiating in the left arm and acroparesthesia of the fingers and toes. A cervical MRI was performed to eliminate the suspicion of cervical spondylotic myelopathy.

Due to persistent acroparesthesia, a nerve conduction study was performed in 2013, revealing an axonal sensorimotor polyneuropathy.

In 2016, the echocardiography revealed small pericardial effusion with fibrin strands and early stage pulmonary hypertension.

In November 2016, due to repeated exposure to the cold weather, she begins to develop painful erythrocyanotic skin plaques, complicated with ulcerations, on the fingers, toes, nose and on the malar region of the face (Fig. 2). The patient administered, on her own, topical corticosteroids and topical antibiotic, with resolution of the skin lesions within 3-4 weeks. In February 2017, on the periodic evaluation, the diagnosis of pernio-like lesions was formulated. The physical exam found skin scarring on those mentioned areas.

As previously mentioned, in July 2018 the woman is admitted again at the hospital for reevaluation, this time accusing also, inflammatory pain and stiffness of the shoulder and hip girdle. We performed a musculoskeletal ultrasound which revealed right im-



FIGURE 2. Photos of the skin lesions on the face and fingers (taken by the patient at the onset)

pingement syndrome, mild subacromial bursitis, mild subdeltoid bursitis (Fig. 3), subscapular tendinitis and supraspinatus tendonitis.

Increase in arterial stiffness is suggested by the gradual progression of ankle-brachial index (2.1 left and 1.9 right in 2011 compared to 1.87 left and 1.75 right in 2018). The symptomatic and objective progression of the disease has led to the increase of azathioprine dose to 150 mg/day.

DISCUSSIONS

The onset of Takayasu arteritis is almost always between the age of 10 and 40 years. Juvenile-onset Takayasu's arteritis represents a challenge to the clinician, the world medical literature being scarce. The youngest reported patient was diagnosed at the

age of 6 months (5). Sometimes, the clinical features are non-specific, making the diagnosis difficult.

The largest multicenter study about juvenile-onset Takayasu's arteritis found out that the most common symptoms in baseline assessment are constitutional, neurological and musculoskeletal. Out of the 71 patients selected in the study, 51 of them were girls, showing a higher prevalence in female population. The most frequent finding in laboratory testing was an ESR elevation (9).

Another particularity of this case is the development of pulmonary hypertension as a complication of Takayasu arteritis. There are several pulmonary abnormalities associated with Takayasu arteritis, most of them being asymptomatic (10). Although pulmonary hypertension is rarely associated with

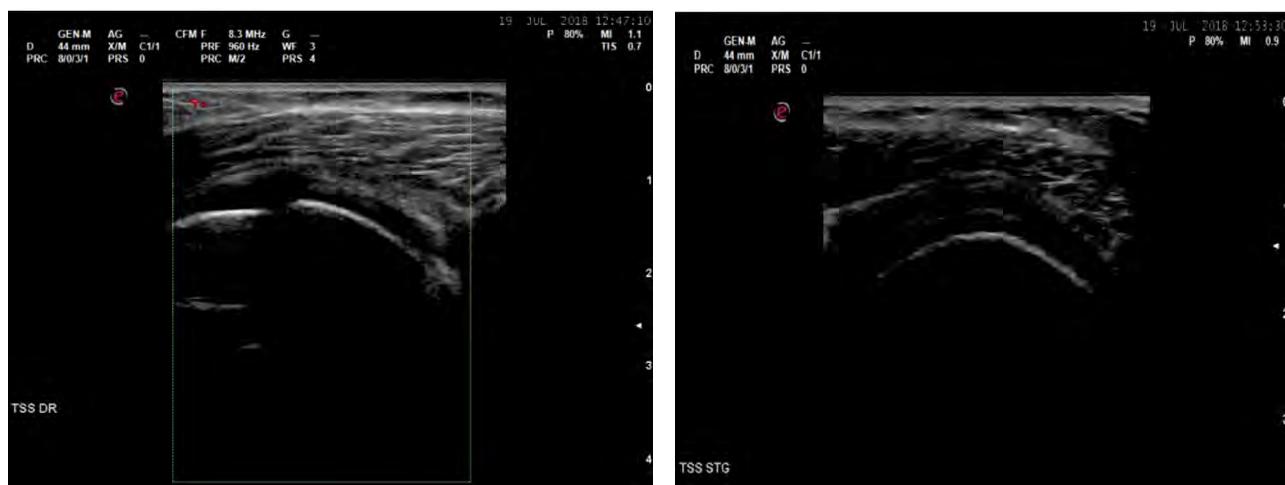


FIGURE 3. Ultrasound findings of subdeltoid bursitis (2018)

Takayasu arteritis, early screening should be applied to all patients (11).

Pernio, also called chilblains, is a localized vasculitis triggered by exposure to cold (12). In contrast with Raynaud phenomena, it is characterized by prolonged vasospasm. There is no clear association between large vessel vasculitis and localized small vessel vasculitis, but immunological mechanisms and poor circulation may be a cause of developing secondary pernio-like lesions.

Although in vasculitis there are multiple autoimmune mechanisms that lead to damage of nervous system, usually, in Takayasu arteritis the peripheral nervous system is not affected. Peripheral neuropathy was only associated until now with giant cell arteritis (13).

Therefore, early pulmonary hypertension, chilblains and peripheral neuropathy coexisting in a patient with Takayasu arteritis is indeed an unusual presentation, raising questions about how much do we really know about the pathophysiology of this disease.

Moreover, the clinical picture of the last hospital admission raises the hypothesis of polymyalgia rheumatica coexisting with a large-vessel arteritis. It is hard to differentiate non-specific arthralgia and myalgia associated with Takayasu arteritis from symptoms of polymyalgia rheumatica. In ultrasound of the shoulder, the most typical findings for polymyalgia rheumatica consist of subdeltoid bursitis and biceps tendon tenosynovitis, one of them being confirmed for our patient (14).

To date there are no specific diagnostic tests, the final diagnostic of polymyalgia rheumatica being based on clinical and laboratory findings, on the re-

sponse to corticotherapy and on the exclusion of other disorders. Several classification criteria were proposed, but none of them have been validated. Usually the age of onset is over 50 years old. (15) Polymyalgia rheumatica is associated with giant cell arteritis in over 50% of cases. Giant cell arteritis is extremely rare before 50 years of age, the first youngest biopsy-proven case being reported in 2006 in Journal of Vascular Surgery at the age of 17 years. Symptoms include temporal artery tenderness, malaise and localized headache (16,17).

The question whether Takayasu arteritis, giant cell arteritis and polymyalgia rheumatica are different medical conditions or represent a spectrum of the same disease was first raised in 1973 by Hall, G. in American Heart Journal. Even though further studies are required to determine if these diseases have the same pathophysiologic mechanism, some scientists sustain the idea that one patient can associate the three conditions in different stages of his life. Moreover, differentiating Takayasu arteritis from giant cell arteritis that has no cranial involvement can be a challenge, as symptoms and histopathological findings are often similar (18).

CONCLUSION

To summarize, this case underlines the importance of further studies for establishing not only classification criteria, but diagnostic criteria of early-onset vasculitis and also for understanding the molecular mechanisms of these diseases. Until then, the question of whether Takayasu arteritis, Giant cell arteritis and polymyalgia rheumatica are or are not a spectrum of the same disease remains unanswered.

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