Isoniazid-induced Takayasu arteritis remission

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SUMMARY

A 75-year-old man was admitted because of fever, unproductive cough, neck pain and upper limb claudication. The patient was febrile and hypotensive, and a cardiac systolic ejection murmur was heard. Blood tests showed normochromic anemia, elevated erythrocyte sedimentation rate, C-reactive protein, fibrinogen, and alpha-2 and beta-2 globulins. In order to investigate neck pain, an ultrasound examination of the carotid arteries was performed which showed a carotid intima-media thickness reaching the maximum value of 2.3 mm in both carotid arteries. Ultrasound examination of the temporal artery and its rami demonstrated wall thickening, both in the common superficial temporal artery and its frontal and parietal rami. A temporal artery biopsy was performed and was consistent with Takayasu arteritis. A positive interferon-γ release assay revealed latent tuberculosis infection and isoniazid 300 mg every 24 hours was commenced. Neither corticosteroids nor other drugs were prescribed at that time. Two weeks later, ultrasound examination showed a significant reduction in the thickening of all investigated arteries. To our knowledge, this is the first case of isoniazid-induced Takayasu arteritis remission. We believe that isoniazid deserves further investigation regarding its potential immunomodulatory properties.

Keywords: Takayasu arteritis, isoniazid, remission.

INTRODUCTION

Despite several assumptions, etiology of Takayasu arteritis (TA) is still unclear. The involvement of mycobacteria has long been suspected but has not been incontrovertibly proven. TA treatment may include dapsone, usually prescribed to treat leprosy, as a steroid-sparing agent. We reported the first case of another agent active against mycobacteria, isoniazid, inducing TA remission, suggesting further investigation on its immunomodulatory effect.

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CASE REPORT

A 75-year-old Italian man with no comorbidities was admitted because of a 12-weeks history of fever, unproductive cough, neck pain, right upper limb claudication and weight loss. On clinical examination, the patient was febrile (37.8°C), hypotensive (90/60 mmHg), with a normal heart rate (76 beats per minute). A cardiac 2/6 systolic ejection murmur corresponding to pulmonary valve was heard. Blood tests showed normochromic anemia (Hb 10.9 g/dL, MCV 89 fL), hypoalbuminemia (3 g/dL) and elevated C-reactive protein (151 mg/L), erythrocyte sedimentation rate (85 mm/first hour), fibrinogen (963 mg/dL), ferritin (1234 ng/mL) and alpha-2 and beta-2 globulins. Blood, urine and stool cultures were negative. Widal-Wright test, HIV and *Borrelia* serology as

well as antinuclear antibodies, rheumatoid factor, anti-neutrophil cytoplasmic antibodies, anti-cardiolipin antibodies were negative. Electrocardiogram and echocardiography were normal.
Ultrasound (US) examination was performed to investigate the neck pain. US examination of carotid arteries showed a carotid intima-media thickness (C-IMT, corresponding to the distance between the blood-intima and media-adventitia interfaces) of 2.3 mm, in both carotid arteries. A wall thickening, including the intima, media, adventitia and temporal fascia, both in common superficial temporal artery (2.4 mm, compared to 1.7±0.3 mm in non-pathological condition) and its frontal and parietal rami (1.2 mm, compared to 0.8±0.2 mm in non-pathological condition) was found [1]. In the frontal ramus the halo sign was also present (Figure 1a-b).
A temporal artery biopsy was performed showing a remarkable thickening of the arterial wall, with luminal narrowing and lymphocytic infiltrate in the internal and external elastic foil. The vessel wall histopathological examination showed an increased cellularity and multinucleated giant cells with granulomas were demonstrated (Figure 1c).
A total body 18-FDG-PET-CT was performed which showed an abnormal radionuclide concentration in the aorta ascending wall (SUV 4.2), abdominal aorta (SUV 4.1), brachiocephalic trunk and subclavian arteries (SUV 4.4), carotid arteries, iliac and femoral arteries (SUV 4.0) (Figure 2).
TA was diagnosed according to Ishikawa's diagnostic criteria modified by Sharma et al. [2]. Sharma's criteria include three major criteria and ten minor criteria (Table 1). TA is highly probable when there are at least two major criteria, one major and two minor criteria or four minor criteria. Our patient had two major (right and left mid

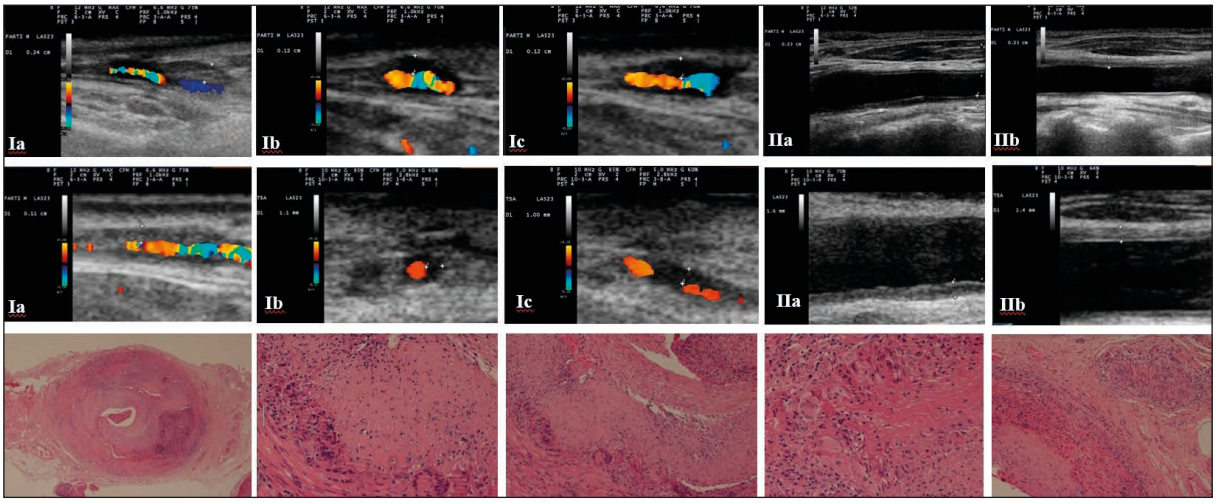

Figure 1a - Longitudinal axis US examination on admission (high-resolution linear probe).
I: Superficial temporal artery. Common superficial temporal artery wall (in normal subjects 1.7±0.3 mm) was 2.4 mm (Ia). The wall of the frontal (Ib) and parietal (Ic) rami (in normal subjects 0.8 ±0.2 mm) was 1.2 mm.
II: Common carotid arteries. The C-IMT of the right common carotid was more severe on the anterior side, with a maximum value of 2.3 mm (IIa). The C-IMT of the left common carotid was more important on the posterior side, with a maximum value of 2.3 mm (IIb).

Figure 1b - US examination at first revaluation (after two weeks of isoniazid treatment).
I: Superficial temporal artery. Wall thickness reduction of the common superficial temporal artery (1.3 mm) (Ia), of the frontal ramus (0.1 mm) (Ib) and parietal ramus (0.2 mm) (Ic).
II: Common carotid arteries. C-IMT reduction in both arteries: anterior side of the right common carotid artery of 0.9 mm (IIa), posterior side of the left common carotid artery (0.7 mm) (IIb), in comparison to the C-IMT before isoniazid.

Figure 1c - Temporal artery biopsy. Arterial wall thickening, with multinucleated giant cells forming granulomas with focal necrobiosis. It is possible to notice luminal narrowing and lymphocytic infiltrate fragmenting the internal and external elastic foils and extending to the adventitia.

US = Ultrasound. C-IMT = Carotid intima-media thickness.

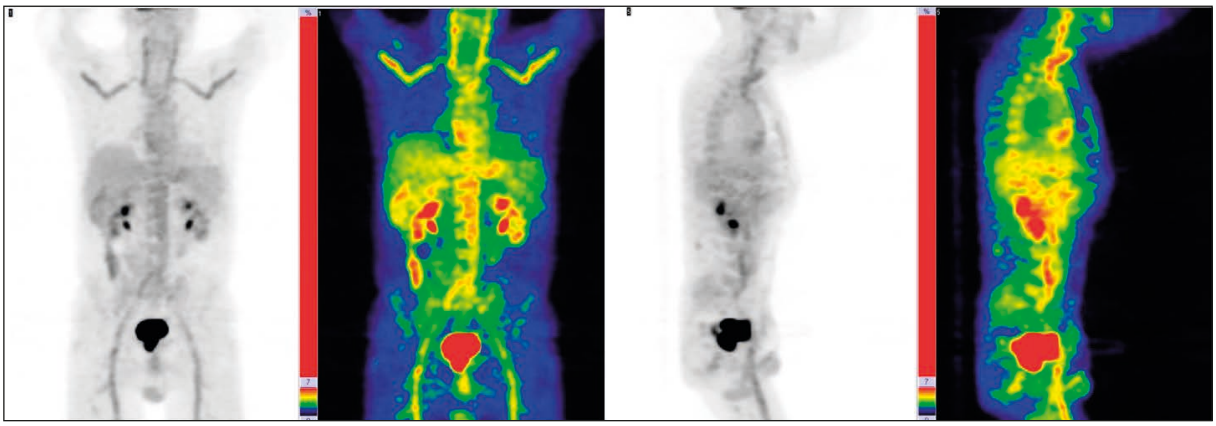

Figure 2 - Total body 18-FDG-PET-CT showing hypercaptation of radiotracer in the ascending and abdominal aorta, brachiocephalic trunk and subclavian arteries, carotid arteries, iliac and femoral arteries. Involvement of both subclavian arteries contributed to the diagnosis of Takayasu arteritis.

FDG = Fluorodeoxyglucose. PET = Positron Emission Tomography. CT = Computed Tomography.

subclavian artery lesion) and four minor (high erythrocyte sedimentation rate, left mid common carotid stenosis, distal brachiocephalic trunk stenosis, abdominal aorta lesion) criteria.

A chest radiograph and a thoraco-abdominal computed tomography were performed and showed no pathological findings. The patient was diagnosed with latent tuberculosis infection (LTBI) after a positive interferon-γ release assay (IGRA), routinely performed in our hospital when an immunosuppressive treatment is planned. Following diagnosis, a therapy with isoniazid 300 mg orally every 24 hours was commenced. Until first revaluation the only prescribed drug was isoniazid. In order to investigate the presence of *Mycobacterium tuberculosis* DNA, a polymerase chain

Table 1 - Sharma's modified diagnostic criteria for Takayasu arteritis. Adapted from Sharma et al. [2].

Three major criteria	*Left mid subclavian artery lesion* (the most severe stenosis or occlusion present in the mid portion from the point 1 cm proximal to the vertebral artery orifice up to that 3 cm distal to the orifice determined by angiography)
	Right mid subclavian artery lesion (the most severe stenosis or occlusion present in the mid portion from the right vertebral artery orifice to the point 3 cm distal to orifice determined by angiography)
	Characteristic signs and symptoms of at least one month duration: limb claudication, pulselessness or pulse differences in the limbs, >10 mmHg systolic blood pressure difference in limb, fever, neck pain, transient amaurosis, blurred vision, syncope, dyspnea, palpitations.
Ten minor criteria	*High ESR* (>20 mm/h)
	Carotid artery tenderness (on palpation, unilateral or bilateral)
	Hypertension (persistent blood pressure >140/90 mmHg brachial or >160/90 mmHg popliteal)
	Aortic regurgitation or annuloaortic ectasia
	Pulmonary artery lesion (lobar or segmental arterial occlusion or equivalent determined by angiography or perfusion scintigraphy, or presence of stenosis, aneurysm, luminal irregularity or any combination in pulmonary trunk or in unilateral or bilateral pulmonary arteries determined by angiography)
	Left mid common carotid lesion (stenosis or occlusion)
	Distal brachiocephalic trunk lesion (stenosis or occlusion)
	Descending thoracic aorta lesion (narrowing, aneurysm or dilation)
	Abdominal aorta lesion (narrowing, aneurysm or dilation)
	Coronary artery lesion (documented on angiography below the age of 30 years in the absence of other risk factors)

reaction on arterial biopsy was performed. No mycobacterial DNA was detected, in agreement with international literature [3].
At first revaluation, two weeks later, US examination showed a reduction in the wall thickening of 1.3 mm on common superficial temporal artery, and 0.1 mm and 0.2 mm on its frontal and parietal rami respectively. A reduction of C-IMT was evident in both common carotid arteries compared to the same area thickness measured on admission: a decrease of 0.9 mm on right common carotid artery and of 0.7 mm on left common carotid artery was found.
At this point a therapy with steroid and methotrexate was started, in combination with isoniazid. Six months later, the temporal thickness was no longer present in either common, frontal and parietal rami of temporal artery. Halo sign in frontal ramus was no longer detectable, suggesting a full recovery [4]. A normalization of C-IMT was observed in both carotid arteries. Both ultrasound revaluations were performed by the same sonographer.

DISCUSSION

TA, also known as pulseless disease, young female arteritis, middle aortic syndrome and occlusive thrombo-aortopathy, is a chronic disease belonging to the so-called large vessels vasculitis that mainly affects young individuals. It carries an increased risk of cardiovascular diseases, such as vascular claudication, congestive heart failure, neurological ischemic events, accelerated atherosclerosis. The risk of cardiovascular complications increases due to the frequent delay in the diagnosis, as signs and symptoms are often aspecific. The estimated 5-year survival rate is 81-95%, while the 10-year survival rate is around 73-90% [2, 5]. When temporal artery is involved, there might be complications such as damage of the facial nerve, skin necrosis, drooping of the eyebrow, and stroke [1]. Few cases of spontaneous remission of TA have been described, but this is a quite rare event [6-8]. In our patient the quick response (2 weeks) strongly suggests a role of isoniazid in being responsible for the initial remission induction. Isoniazid is a drug active against mycobacteria and these bacteria have long been suspected to be involved in the pathogenesis of chronic granulomatous diseases [9-11].

Khan et al. in 2016 evaluated the prevalence of *Mycobacterium avium subspecies paratuberculosis* (MAP) in intestinal biopsies in patients with Crohn's disease or intestinal tuberculosis using both PCR and immunohistochemistry [9]. MAP was previously known to cause Johne's disease, a chronic progressive granulomatous inflammatory bowel disease in ruminant animals. The authors reported a significantly high prevalence of MAP in patients with Crohn's disease (23.2%, p=0.03) as compared to the controls (7.3%), while non significative difference was observed in patients with intestinal tuberculosis compared to the controls. Nevertheless, these findings have not been supported by further studies. Alba et al. in 2013 reported some cases of disseminated TB concurrent with giant cell arteritis (GCA), recommending to have a high suspicion index for both diseases in elderly presenting with fever of unknown origin, headache, elevated erythrocyte sedimentation rate and visual symptoms [12]. Other authors investigated the connection between *Mycobacteria* spp. and chronic granulomatous disease, finding sometimes conflicting results that, though they do not confirm undoubtedly this connection, they raise suspicion on it [3, 10, 11]. It is worth remembering the study by Karadag et al., in which they assessed the prevalence of LTBI in patients affected by TA, reporting IGRA as a more reliable test compared with tuberculin skin test [13]. Recently, Jansson et al. performed a case-based review and collected eighteen previously published case reports of concomitant active TB and TA [14].
Mycobacteria presence in granulomas has never been proved, but the hypothesis of mycobacteria being somehow involved in chronic granulomatous diseases is reinforced by other evidences [3]. First, it has long been known that giant cells and granulomas in TA and other chronic granulomatous diseases are histologically similar to those found in infections sustained by *M. tuberculosis* and patients with TA are not uncommonly infected with TB, although this association may be casual in high TB incidence countries [11, 15, 16]. Second, Moraes et al. reported an increased response to mycobacterial antigens in patients affected by TA, strengthening the connection between mycobacterial infection and TA [16]. Third, dapsone is an anti-mycobacterial agent commonly used in association with rifampin and clofazimine in the treatment of leprosy [17]. When it

is used in the treatment of large vessels vasculitis and Crohn's disease, it works as a steroid-sparing agent, so it has been supposed that dapsone is effective against the unknown underlying cause of these chronic granulomatous diseases [13, 18]. It is important to notice that while dapsone has a known immunomodulant action, isoniazid does not and this case leads to some considerations.
Our case may support the theory of mycobacteria, maybe resident in another part of the body (*e.g.* gut, lungs, respiratory microbiome in the patient with bronchiectasis), being somehow involved in the pathogenesis of chronic granulomatous diseases, as isoniazid, a drug active against mycobacteria, induced TA remission [19]. In addition, an immunomodulant not yet proven effect of isoniazid, is a possibility that deserves further investigation.

Consent
The patient authorized the doctors to use and publish his disease related article with personal information deleted.

Conflict of interest: The authors declare no conflict of interest.

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