Juvenile arteritis revisited

Buerger's disease – Takayasu's disease

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Abstract

Thromboangiitis obliterans is defined as an inflammatory disease involving small and medium sized arteries and veins. As no clinical symptoms, signs, radiological or laboratory abnormalities nor pathological features are specific, the diagnosis is usually made according to the criteria proposed by Adair in a young smoker, male or female, with distal arterial occlusions sometimes associated with thrombophlebitis and with negative aetiological investigations. Recently, rheumatic manifestations were identified in about 10% of patients. If new developments in vascular medicine, as ultrasound explorations or CT scan limit the indications for angiography, others, especially in the field of thrombophilia, make more difficult the differential diagnosis. If the strong link between the disease activity and smoking habits is confirmed, medical or surgical approach remain disappointing. Takayasu's disease or non specific aorto-arteritis is an inflammatory disease of young women that primarily affects the aorta its main branches and the pulmonary arteries. The disease often start in children. The prevalence of the disease as the arterial lesions show geographical variations. That and the different associations with infectious, rheumatic or systemic diseases could justify to consider Takayasu's disease as a syndrome. B-mode ultrasonography and electron beam computed tomography are usually sufficient to characterize the

arterial involvement and are essential for the follow up of patients. In some rare cases arterial biopsy is necessary to confirm the diagnosis. The surgical treatment concerns specific lesions with ischemic symptoms and failure of the medical approach, however endovascular techniques are often discussed in first intention. During inflammatory phases with evolutive lesions corticosteroids are often used. In case of failure cyclophosphamide or methotrexate have been used.

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Early in the XXth century, in 1908, two inflammatory vascular diseases that specifically concern young people were recognized. The first one was described in New York by Leo Buerger and called thromboangiitis obliterans, the other in Japan by an ophthalmologist M. Takayasu. One century later few is still known concerning the etiopathogenic mechanisms of these two vasculitis. However new imaging techniques give more strong diagnosis criteria and some limited progress for the treatment are emerging.

1. Thromboangiitis obliterans

a. Diagnosis

Thromboangiitis obliterans is defined as an inflammatory disease involving small and medium sized arteries and veins. As no clinical symptoms, signs, radiological or laboratory abnormalities nor pathological features are specific, diagnosis

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Table 1. Scoring system for the diagnosis of thromboangiitis obliterans (4)

Positive points		
Age at onset	Less than 30/30-40 years	+2/+1
Foot intermittent claudication	Present / by history	+2/+1
Upper extremity	Symptomatic / asymptomatic	+2/+1
Migrating superficial vein thrombosis	Present / by history only	+2/+1
Raynaud	Present / by history only	+2/+1
Angiography; biopsy	If typical both / either	+2/+1
Negative points		
Age at onset	45-50/more than 50 years	-1/-2
Sex, smoking	Female, non smoker	-1/-2
Location	Single limb/no LE involved	-1/-2
Absent pulses	Brachial/femoral	-1/-2
Arteriosclerosis, diabetes, hypertension, hyperlipidemia	Discovered after diagnosis 5.1-10 years/ 2.1- 5 years later	-1/-2

is usually founded on a probabilistic approach. Mozes and al in 1970 (1) described criteria for diagnosing Buerger's disease. A patient was considered with a low probability to have thromboangiitis if he was a young male smoker with distal arterial occlusions and with no evidence of arteriosclerosis, hyperlipidemia, diabetes, collagen disease, hematological disorder or a potential source of proximal emboli. If any one of the 3 recognized hallmarks of the disease: superficial vein phlebitis (phlebitis saltans), involvement of the upper limb distal arteries, Raynaud's phenomenon was present, the diagnosis of Buerger's disease was considered as probable, it was considered as definite if two or more criteria were present. Since these reports, an increasing prevalence of thromboangiitis in women has been reported (2) and we have proposed to use Mozes criteria regardless of the sex of the patient (3). We add an important exclusion criteria with the entrapment syndrome of the popliteal artery. More recently, Adar's group proposed a point scored system (table I) (4). It allows to include women however and improves the specificity of diagnosis. There are 6 elements that contribute to positive score and five negative points. In a young patients with distal lower limb ischemia with no evidence of arterioclrosis, hyperlipidaemia, diabetes collagen disease, haematological disorder or a potential source of proximal emboli, scoring is completed after all points have been assigned. The probability of the diagnosis of thromboangiitis is obtained from the arithmetic sum of the points (table II). The possibility to include patients with exclusion criteria developed after diagnosis needs a regular re-evaluation of the initial diagnosis. In a group of 107 patients with a previous diagnosis of thromboangiitis, no less than 20 patients were excluded by the new point system.

Thus in clinical practice, thromboangiitis is confirmed only when all others diagnosis have been ruled out. Ultrasound explorations combined with CT scan permit to exclude atherosclerosis lesions on the aorta and the lower limb arteries and confirm the distal occlusions, often bilateral, of leg arteries. Thus, when the clinical presentation is suggestive, arteriogra-

phy is no more mandatory. The main difficulties concern the relationship between thromboangiitis and some new types of thrombophilia. Theoretically, abnormalities of hemostasis excluded the diagnosis of Buerger's disease. However some disturbing observations of thromboangiitis associated with antiphospholipid antibodies have been reported (5).

b. Rheumatic manifestations

In a retrospective chart review of 83 patients (71 men, 12 women) with a diagnosis of thromboangiitis (6), we found 11 patients (12.5%) with rheumatic manifestations. Compared with the entire cohort, the 11 patients were more often female ($p=0.08$) but no other difference concerning either the clinical or biological characteristics was found. Eight patients presented initial recurrent of arthritis which preceded the first occlusive symptoms by 2 to 11 years (mean 6 years). These episodes were monoarticular, acute, transient and migratory with local inflammatory signs. The wrists and knees were the most frequently involved joints. The duration of signs and symptoms ranged from 2 to 14 days. The arthritis was non erosive, rheumatoid factor and antinuclear antibodies were not detected. Two patients had HLA B27 positive undifferentiated spondyloarthropathies. The last patient presented initial transient asymmetric oligoarthritis affecting the ankles, knees, and the left wrist. Synovial fluid obtained by right knee arthrocentesis contained a large amount of polymorphonuclear leukocytes. The description of rheumatic manifestations in thromboangi-

Table 2. Sum of points defines the probability of the diagnosis of Thromboangiitis obliterans (4)

Number of points	Probability of diagnosis
0-1	Diagnostic excluded
2-3	Suspected, low probability
4-5	Probable, medium probability
6 or more	Definite, high probability

itis has, at least two outcomes: Firstly it confirms the specificity of Buerger's disease as a systemic vasculitis, secondly rheumatologist have to consider the diagnosis in young smoker patients with intermittent rheumatism.

c. Treatment

If the strong link between the disease activity and smoking habits is confirmed, the etiopathogenic mechanism of Buerger's disease is still unsolved. Thus stopping smoking is actually the most essential feature of treatment. The frequency of vasomotor events preceding the disease (7) have led to consideration of the role of spasm in the pathophysiology of the vascular disease and calcium inhibitors are often advocated even though their is no proof of their efficacy. Although thromboangiitis obliterans is considered as a vasculitis, there is actually no indication for the use of immunosuppressive drugs. Despite the constant finding of both arterial and venous thrombosis, coagulation abnormalities have never been demonstrated. Thus anti-thrombotic drugs have no place in the treatment of Buerger's disease.

After stopping smoking, local treatment of cutaneous lesions is the second most important part of management. Hospitalisation in vascular medicine department is required.

Following some anecdotal reports of success in treating thromboangiitis with pro-staglandins, the Milestone study (8) compared a 6 hour intravenous infusion of iloprost (a chemically stable prostacyclin analogue) with low dose of aspirin. It was a double blind multicenter controlled study. It included 152 patients with Buerger's disease with rest pain with or without trophic lesions. Treatment lasted for 21 to 28 days with reassessment at six month. Evaluation of therapeutic efficacy was based upon changes in pain, trophic lesions, analgesic consumption and overall improvement with classification into responder and non-responder patients as endpoint (table III). At the end of the infusion 58 of the 65 patients treated with iloprost (85 per cent) as compared with just 11 (17 per cent) of those treated with aspirin were classified as responders. Complete relief of pain was achieved in 63% of patients treated with iloprost compared with 28% of patients on aspirin. Among patients with trophic changes, 35% on iloprost achieved complete healing compared with 13% of aspirin. Five months later, 95 patients were seen again and the difference in term of responder was still significant in favour of the treatment of iloprost. Of the 133 patients, 11 underwent amputation. Two patients in each group underwent distal amputation during the month of the infusion. One patient only, in the aspirin group, had a distal amputation during the follow-up. Six high amputations were carried out: one thigh amputation in the iloprost group compared with five leg amputations in the aspirin group. However the results of a randomised placebo-controlled study comparing oral iloprost twice daily versus placebo were a little more disappointing (9). Three hundred and nineteen patients with Buerger's disease were randomised between placebo, oral iloprost 100µg twice daily, oral iloprost 200µg twice daily. Total healing of lesions, the primary endpoint, was not significantly different between treatment groups

at the end of treatment neither at six months. The low dose of iloprost was significantly more effective than placebo for relief of rest pain without analgesic at the end of the follow up but not at the end of treatment. Low dose iloprost was also effective at 8 weeks and at 6 months on the combined end point (alive without major amputation, no lesions, no rest pain, no analgesic). However, high dose iloprost failed to show significant treatment effects over placebo.

In 1998 Isner and al (10) reported the use of intramuscular injections of VEGF in six patients, 7 limbs, with Buerger's disease and critical ischemia. These preliminary results document augmented perfusion in all the limbs, the ulcers healed completely in 3 of 5 limbs in 4 patients, nocturnal rest pain was relieved in 2 patients. However 2 patients required below knee amputation. At the present time sympathectomy is usually considered after failure of medical treatment before or as-associated with an amputation. Shionoya (11) reported success in revascularization in patients with thromboangiitis. In most instances, bypass procedures are impractical or long term success are poor because a poor sites for the distal anastomosis and poor distal runoff. However if a patient has critical ischemia and there is a distal target vessel, bypass surgery with the use of an autologous vein should be considered.

2. Takayasu's disease

Takayasu's disease is an inflammatory disease of young women that primarily affects the aorta its main branches and the pulmonary arteries. The disease often start in children. The prevalence of the disease as the arterial lesions show geographical variations. That and the different associations with infectious, rheumatic or systemic diseases could justify to consider Takayasu's disease as a syndrome, as pointed by the term non specific aorto arteritis.

a. Diagnosis

The topography of arterial lesions is the most important criteria for the diagnosis. Thus Lande proposed toto-aortography as gold standard for diagnosing Takayasu's arteritis (12). However, angiography is invasive and does not show the wall thickening, a major distinguishing criteria. In a prospective

Table 3. Iloprost versus Aspirin in Buerger's disease: results on intention to treat analysis (8)

Iloprost	Aspirin		
		N=68	N=65
At day 28			
Responders		58 (85%)	11 (17%)
Total relief of rest pain		43 (63%)	18 (28%)
Complete healing of all trophic changes		18/52 (35%)	6/46 (13%)
		—	
At 6 months from start of treatment		N=51	N=44
Responders		45 (88%)	12 (21%)
amputations		3 (6%)	8 (18%)

study (13), we have assessed in 43 patients with known Takayasu's disease, the value of B-mode ultrasonography (B-mode US) associated to electronbeam computed tomography (EBCT). Six sites were examined by B-mode US: left and right common carotid, subclavian and common femoral arteries. Five sites were analysed by EBCT pulmonary arteries, aortic arch, ascending and descending thoracic aorta and abdominal aorta.

B-mode ultrasound detected the characteristic wall thickening in all patients but one (98%) (table IV). All patients but two (95%) had a lesion (stenosis, occlusion, aneurysm or wall thickening) of the subclavian and/or common carotid arteries. Five patients had no lesions detectable by electron-beam computed tomography. Wall changes was the most frequent lesion detected in 29 patients (71%). Stenoses were visualized in 13 patients mainly in the descending and abdominal aorta. Aneurysms were seen in 28 (68%) patients mainly on the pulmonary artery and thoracic aorta. The total number of sites studied by B-mode US and EBCT in each patients was 11. The combined results of the two technics showed that all patients

have at least one abnormal sites with a median score of 7 abnormal sites. Thus B-mode US and EBCT was able to visualize the classical calibre abnormalities and depicted in contrast to angiography vessel wall thickening. EBCT detected pulmonary artery involvement very suggestive of Takayasu's arteritis and asymptomatic in most cases. In 16 patients (14) we have shown that EBCT can demonstrate mural and luminal changes over time and thus can be used for the follow-up of patients.

In some rare cases clinics and arteriographics criteria do not permit the diagnosis, in these cases an arterial biopsy is sometimes necessary. Takayasu's disease is characterized histopathologically by a chronic arteriopathy which progresses from the outer part of the vessel wall and leads to luminal occlusion. Most changes are found in the adventitial and medial layers with a tremendous thickening of the adventitial by dense collagenous tissue destroying the external part of the media. We have shown that this aspect permit a clear distinction with lesions affecting mainly the media and the internal elastic lamina in temporal arteritis (15).

b. Treatment

The surgical treatment concerns specific lesions with ischemic symptoms and failure of the medical approach. Endovascular techniques are often discussed in first intention (16). However, an important limitation is the high incidence of restenosis related to the activity of the disease. The long term efficacy of stent placement needs to be evaluated.

The decision for corticosteroids or more aggressive immuno-suppressive drugs is usually done on the demonstration of a progression of arterial lesions (17). The relationship between clinical or biological parameters and the evolution of the disease is poor, thus the use of CT scan and B-mode US could be useful for evaluating response to treatment (14).

Table 4. Frequency of involved sites detected by B-Mode US and EBCT in 43 Takayasu's arteritis patients (13)

B-MODE ULTRASONOGRAPHY (41 patients)	
Wall thickening	40 (98%)
Subclavian arteries involvement	28 (70%)
Common carotid arteries involvement	26 (95%)
Common carotid and/or subclavian arteries	39 (95%)
ELECTRON BEAM COMPUTER TOMOGRAPHY (41 pat.)	
Wall thickening	29 (71%)
Stenoses	13 (32%)
Aneurysms (pulmonary and thoracic aorta)	28 (68%)
Every patients had at least one abnormality of the studied sites	

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