Clinical, Arteriographic and Histopathologic Analysis of 13 Patients with Thromboangiitis Obliterans and Coronary Involvement

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ABSTRACT: Smoking is a risk factor for thromboangiitis obliterans (TAO, Buerger's disease) and arteriosclerosis, but there are few cases of coronary heart disease (CAD)-associated Buerger's disease. A literature search for articles in English, Spanish and French published between 1966 and 2012 on patients with coronary involvement and TAO revealed 12 patients. We describe an additional case with involvement of the central nervous system, myocardium and large-diameter proximal arteries. The main clinical manifestations in these 13 cases were lower limb claudication and acute thoracic pain. The histologic findings showed thrombosis with unbroken internal elastic lamina and intimal clusters of granulocytes; coronary angiography revealed predominant involvement of the left anterior descending and right coronary artery. Treatment included coronary bypass procedures, coronary angioplasty, smoking cessation, and anticoagulant therapy. A complete therapeutic response was observed in half the patients. This review of all published cases of TAO patients with coronary symptoms, together with our patient, demonstrates the rarity of this clinical association. Patients under age 40 with CAD but no prominent cardiovascular risk factors besides smoking should be evaluated for the presence of Buerger's disease.

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KEY WORDS: thromboangiitis obliterans (TAO), coronary heart disease, cardiovascular disease, vasculitis, smoking

Thromboangiitis obliterans or Buerger disease is a non-necrotizing vasculitis that affects small and medium-sized arteries, typically in young male smokers, with onset of symptoms before age 45 years [1]. Exposure to tobacco is strongly associated with the occurrence of TAO, suggesting that smoking plays a role in the pathogenesis of the disease [2]. TAO was found in 0.5–5% of hospitalized patients with arterial occlusive disease in Europe [3-6] and up to 16% of patients in Japan [7]. It can affect all races [8].

Although the disease involves the arteries of the extremities, characterized by ulcerations, ischemia and limb claudication, in some rare cases the coronary, carotid and arteries of some internal organs may be involved [1]. Patients under 40 years old with coronary artery disease but no prominent cardiovascular risk factors besides smoking should be evaluated for the presence of TAO [1]. This disease can be distinguished from other types of vasculitis by arteriographic and histologic analyses, by the lack of systemic symptoms and specific immunological markers, and normal levels of acute-phase reactants [2]. A pathologic indication is the presence of cellular and inflammatory thrombi with relative sparing of the blood vessel wall [2]. The normal structure of the vessel wall, including the internal elastic lamina, generally remains intact [2]. This feature distinguishes TAO from arteriosclerosis and from other types of systemic vasculitis in which there is usually a striking disruption of the internal elastic lamina and media [9].

Smoking is a risk factor for TAO and arteriosclerosis, but few cases of coronary heart disease-associated TAO have been reported [2]. In light of this, the current article describes the clinical, angiographic, histologic and developmental characteristics of patients with TAO and coronary involvement, and presents an additional patient with TAO, visceral manifestation in the central nervous system and myocardium, and involvement of proximal arteries of large diameter.

BIBLIOGRAPHIC REVIEW

We systematically searched PubMed for English, Spanish and French articles published between 1966 and 2012 on the subject of coronary involvement and concomitant TAO [Table 1] [10,11]. The keywords used were coronary involvement, cardiovascular diseases, coronary heart disease, vasculitis and thromboangiitis obliterans. The articles found were reviewed for demographic characteristics (gender, age), clinical characteristics (clinical presentation of TAO, onset of symptoms,

TAO = thromboangiitis obliterans

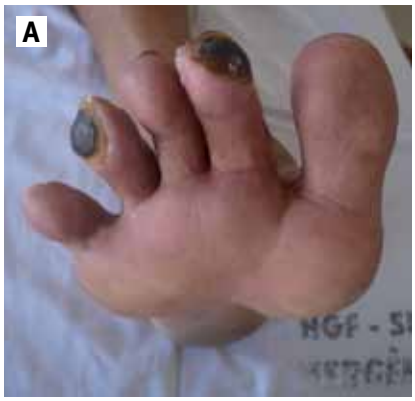
Table 1. Diagnostic criteria for Buerger's disease [4,10,11]

At least two of the following three symptoms	After exclusion of the following conditions
Superficial thrombophlebitis	Diabetes mellitus
Arterial upper limb involvement	Arterial upper limb involvement
Raynaud's phenomenon	Atheromatous lesions
	Potential source of embolism
	Entrapment syndrome
	Autoimmune diseases
	Myeloproliferative syndrome
	Hypercoagulability states

A definitive diagnosis of Buerger's disease was observed in young smokers with distal lower limb ischemia. The presence of any one of these symptoms supports the diagnosis

evolution), treatment, laboratory characteristics, immunologic markers, imaging tests (arteriography of limbs, coronary angiography), and histologic findings. Of the 21 articles found, we excluded 9 because they did not present a well-structured paper that would answer our study questions or were published in a language other than English, Spanish or French.

Smoking is a risk factor for thromboangiitis obliterans and arteriosclerosis



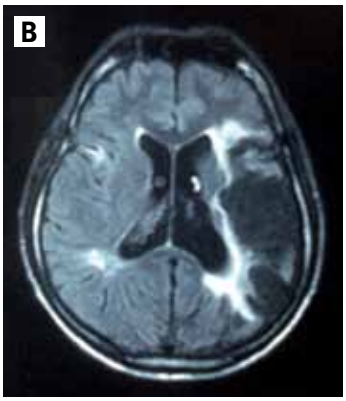
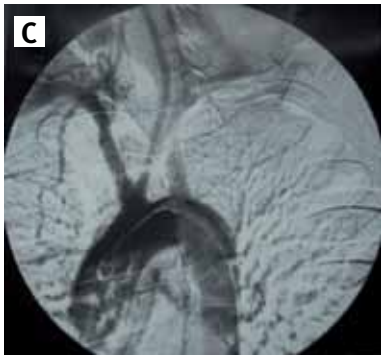


Figure 1. [A] Necrotic lesions in second and fourth toes of the right foot

[B] MRI showing ischemic brain damage with sequelae in the left hemisphere



[C] Arteriography with occlusion of the right carotid and left subclavian artery

[D] Arteriography showing occluded arteries and "corkscrew" infragenicular vessels

ADDITIONAL CASE

We describe a new case of TAO and coronary involvement. This 47 year old male patient presented with complaints of cyanosis, edema, pain and necrosis of the toes of his right foot of 2 months duration. He had a history of limb claudication from the age of 27 and had experienced an ischemic stroke at age 30 with sequelae of dysarthria and right hemiparesis. He had smoked for 37 years. There was no history of hypertension, diabetes or dyslipidemia. On admission, in addition to the neurologic sequelae to the stroke, there was evidence of necrotic lesions on the second and fourth right toes [Figure 1A], signs of thrombophlebitis in the upper limbs, and absence of a pulse in the upper and lower limbs. Laboratory evaluation showed normal inflammatory activity tests, blood count and renal function. Glucose (89 mg/dl), uric acid (7.0 mg/dl), triglycerides (140 mg/dl), total cholesterol (180 mg/dl) and low density lipoprotein (90 mg/dl) were normal. Tests for lupus anticoagulant, anticardiolipin immunoglobulin G and M, prothrombin gene mutation and factor V Leiden mutation were negative. Homocysteine level was 11.6 mmol/L. Urine analysis did not show any change. Tests for viral hepatitis B and C, human immunodeficiency virus, antinuclear antibody, rheumatoid factor, and anti-neutrophil cytoplasmic antibodies were negative. Magnetic resonance imaging showed ischemic brain damage with sequelae in the left hemisphere [Figure 1B]. Carotid Doppler examination showed total occlusion of the right carotid and no signs of an atheromatous carotid artery. Transthoracic echocardiogram showed mild diastolic dysfunction and fibrosis of the anterior wall of the left ventricle. Coronary angiography revealed partial occlusion (70%) of the left anterior descending coronary artery. Arteriography demonstrated occlusion of the right carotid, left subclavian, femoral and left fibula arteries, and presence of "corkscrew" infragenicular vessels [Figures 1C and D].

Histopathology of the superficial veins of the upper limbs showed thrombi with intense intraluminal neutrophilic infiltrate, intact internal elastic lamina and tunica media, consistent with thromboangiitis obliterans. Aspirin treatment was started and the patient was advised to stop smoking. Two months after discharge, the ulcers in his lower limbs had regressed, as did the symptoms of limb claudication; however, the patient continued to smoke regularly. He was subsequently readmitted with chest pain and was hospitalized in the coronary intensive care unit with a diagnosis of acute myocardial infarction. He died two days later.

BACK TO THE REVIEW

The demographic, clinical and histologic characteristics of the 13 patients with TAO and coronary involvement are shown in

Table 2. Clinical and demographic characteristics and histologic findings of the 13 patients with TAO and coronary involvement

Author year [ref]	Age (yr)	Gender	Clinical presentation	Histologic findings
Becit et al. 2002 [1]	36	M	Distal arterial occlusions 12 years prior to acute myocardial infarction	Endarterectomy specimen: marked inflammatory cell infiltration, intimal thickening, proliferation of elastic fibers
Kakihana et al. 2009 [12]	29	M	Thoracic pain and lower limb claudication	N/A
Hsu et al. 2008 [13]	32	M	Acute thoracic pain	N/A
Hong and Faxon 2005 [14]	61	M	Limb claudication and acute thoracic pain	N/A
Heno et al. 2000 [15]	33	M	Limb claudication and ischemic ulcers. Two previous transient ischemic attacks and coronary disease resulting in myocardial infarction	N/A
Harten et al. 1996 [16]	36	M	Myocardial, splenic and cerebral infarctions, pulmonary embolisms and intestinal ischemia	N/A
Kim et al. 1987 [17]	29	M	Chest pain	N/A
Ohno et al. 1986 [18]	33	M	Acute chest pain	N/A
Donatelli et al. 1997 [19]	39	F	2 year history of epigastric pain of unknown origin and sporadic episodes of typical angina for previous 8 months. No evidence of peripheral vascular disease	Internal thoracic arteries occluded by organized thrombosis with intact internal elastic lamina and tunica media. Saphenous vein with intimal clusters of granulocytes and superimposed mural thrombosis
Umami et al. 1999 [20]	63	M	Acute thoracic pain and healed ischemic lesions of foot	N/A
Korsgaard et al. 1988 [21]	53	M	N/A	Characteristic features of TAO
Rodrigues-Fernandez et al. 2002 [22]	56	M	Antecedents of extensive myocardial infarction. Symptoms and signs of ischemic cardiomyopathy and limb claudication	N/A
Nobre et al. 2014 [present study]	47	M	Necrotic lesions in 2nd and 4th right toes. Ischemic stroke with hemiplegia to right lower limb, claudication and thrombophlebitis of upper extremities	Superficial vein of upper limbs: thrombi with intense intraluminal neutrophilic infiltrate

M = male, F = female, N/A = not available or not performed

Table 2, and the angiographic results, treatment and therapeutic responses of these patients are summarized in Table 3. There were only 12 reported cases of TAO associated with coronary involvement in the international literature from 1966 to 2012 [1,12-22]. We excluded nine case reports that did not have the clinical characteristics we were seeking. Our patient with TAO associated with coronary involvement brings the total to 13 cases.

Angiography revealed predominant involvement of the left anterior descending artery in 77% of cases

The patients ranged in age from 29 to 63 and were predominantly male (12/13). The main clinical manifestations were lower limb claudication (5/13) and acute thoracic pain (10/13). The histologic findings (4/13) showed thrombosis with intact internal elastic lamina and tunica media associated with intimal clusters of granulocytes. Coronary angiography revealed predominant involvement of the LAD artery (10/13) and right coronary artery (3/13), and one patient presented with normal arteriography. Treatment included a coronary bypass procedure (2/13), urokinase (1/13), coronary angioplasty (1/13), smoking cessation (5/13) and anticoagulant therapy (4/13), and one patient underwent granulocyte colony-stimulating factor-mobilized peripheral blood mononuclear cell transplantation. Generally, the therapeutic response was satisfactory, with complete improvement in 7 of the 13 patients. No report was available for 3 patients, and 2 patients died. In those who died the clinical presentations were characterized as multiple involvement (splenic, myocardial, cerebral, pulmonary).

LAD = left anterior descending

DISCUSSION

The present study adds a new case of TAO and coronary involvement to the 12 patients previously described [1,12-22]. This is the first article to review the clinical, angiographic, histologic and therapeutic characteristics of patients with coronary involvement and TAO.

Coronary involvement is a rare complication of TAO. Coronary artery disease is generally associated with arteriosclerosis [23]. The major risk factor for TAO and arteriosclerosis is ongoing tobacco exposure [2]. TAO must be differentiated from

Table 3. Imaging tests, treatment and therapeutic response in the 13 patients with TAO and coronary involvement

Author year [ref]	Imaging tests	Treatment	Therapeutic response
Becit et al. 2002 [1]	Total occlusion of proximal segment of LAD and RCA. Ventriculography detected left ventricular dysfunction	Endarterectomy and complex bypass procedure to LAD. Aorta RCA bypass was also applied	Complete improvement
Kakihana et al. 2009 [12]	Echocardiogram demonstrated diffuse hypokinesis and dilated left ventricle. Coronary angiography revealed no organic stenotic lesion	G-CSF-PBMNC transplantation in right leg	Both ischemic symptoms and cardiac symptoms disappeared
Hsu et al. 2008 [13]	Thrombus inside proximal LAD	Coronary angioplasty and stenting successfully performed after thrombus aspiration	Complete improvement
Hong and Faxon 2005 [14]	Total occlusion of proximal segment of LAD	Carotid endarterectomy and smoking cessation	N/A
Heno et al. 2000 [15]	Narrowing of second segment of LAD, occluded distally	Anticoagulant therapy and advised to stop smoking	Complete improvement
Harten et al. 1996 [16]	N/A	N/A	N/A
Kim et al. 1987 [17]	Partial segmental occlusion of LAD at a proximal segment	Vasodilator and anticoagulant therapy and advised to stop smoking	No complications after conservative treatment
Ohno et al. 1986 [18]	70% diameter narrowing in distal RCA and proximal LAD. Angiographic appearance of these lesions suggestive of thrombus. Left ventriculogram revealed akinesia in the anteroapical wall and hypokinesia in the inferior wall	Urokinase, vasodilation and anticoagulant therapy, and advised to stop smoking	Coronary angiography repeated 4 weeks after onset of AMI. Thrombi of right and left coronary arteries resolved. Left ventriculogram same as during acute phase
Donatelli et al. 1997 [19]	Cardiac catheterization showed severe left main disease and critical stenoses of RCA	Three coronary arteries bypassed with saphenous veins	At 8 months follow-up, patient doing well and free of recurrent angina
Umami et al. 1999 [20]	Coronary angiography showed long lesion in LAD	N/A	N/A
Korsgaard et al. 1988 [21]	Scintigraphic signs of infarction in lung and spleen	N/A	Died
Rodrigues-Fernandez et al. 2002 [22]	Coronary angiography suggesting presence of thrombi inside LAD, of gracile aspect (corkscrew image), severe and diffusely obstructed (80%), and poor distal vascular bed	N/A	N/A
Nobre et al. 2014 [present study]	Occlusion of right carotid, left subclavian, superficial femoral and left fibular arteries in presence of image "corkscrew" infragenicular vessels. Partial occlusion (70%) of LAD	Anticoagulation with warfarin and smoking cessation	Died

RCA = right coronary artery, G-CSF = granulocyte colony stimulating factor, PBMNC = mobilized peripheral blood mononuclear cells, LAD = left anterior descending artery, N/A = not available or not performed, AMI = acute myocardial infarction

thrombosis, emboli, arteriosclerosis and forms of arteritis, including periarteritis nodosa, Churg-Strauss disease and Takayasu's arteritis in which coronary artery occlusion may occur [1]. In contrast to TAO, arteriosclerosis is seen among older patients (> 40 years) and there is no significant gender difference [1]. Specific arteritis, as in syphilis and tuberculosis, can be distinguished from TAO by the formation of granulomas, and periarteritis nodosa frequently results in aneurysms following medial and intimal necrosis and involves other layers of vessels [1]. Buerger's disease is a vasculitis characterized by the total occlusion of vessels following intimal swelling, thrombus formation and fibrosis of distal post-stenotic vessels [1]. Nevertheless, in arteriosclerosis, the swollen and hyalinized intima is calcified and contains lipids and cholesterol [1]. Systemic signs and symptoms are extremely rare in patients with TAO [16].

When myocardial infarction occurs in young patients without clinical evidence of cardiovascular disease TAO should be considered

While the histopathologic effects of Buerger's disease on small vessels in the extremities have been well documented, little is known about the involvement of coronary arteries in patients with Buerger's disease [23]. It remains controversial whether coronary artery narrowing in this disease is due to atherosclerosis, a non-atherosclerotic inflammatory process, or a combination of both [23].

A causal association between Buerger's disease and coronary heart disease is rare and difficult to prove in the absence of histopathologic and immunologic tests. Coronary angiography data have not been conclusive regarding a common origin for both diseases [18]. However, in our review, we observed that angiography revealed predominant involvement of the LAD artery in 77% of the cases. Therefore, the occurrence of myocardial infarction and the angiographic appearance of the LAD artery raise the question of coronary involvement in Buerger's disease [15]. To that end Mautner et al. [24] investigated a series of 12 patients with Buerger's disease and performed coronary histology at the time of autopsy. In 9 of the 12 patients, coronary luminal narrowing was due to atherosclerosis, old thrombi were

noted in 7 of the 12, and 5 also had evidence of recent thrombi in one or more coronary arteries. Interestingly, 5 of the 12 patients had evidence of both atherosclerosis and thrombosis in one or more coronary arteries, suggesting that coronary luminal narrowing was a result of both atherosclerosis and thrombus formation.

The arterial involvement in TAO is highly segmental, with abrupt vascular occlusions interspersed with vessels that appear angiographically normal [25]. Also, the angiographic image showing the corkscrew appearance of the coronary artery and intraluminal thrombi suggest thromboangiitis dissemination to the coronary arterial bed [26].

Our case report demonstrates the involvement of the brain; the coronary, subclavian, carotid, femoral and fibular arteries; and vessels with a corkscrew appearance on arteriography of the lower limbs. The diagnosis of coronary involvement in TAO in our patient would depend on a histopathologic examination of the coronary arteries. However, some data point to this diagnosis: namely, the absence of cardiovascular risk factors other than smoking, the onset of symptoms at age 27, the exclusion of other vasculites or thrombophilia, and the fact that the superficial veins of the upper extremity were involved.

Our study had some limitations, such as the absence of histopathologic evidence of TAO in coronary arteries and the absence of universally accepted diagnostic criteria [10]. Moreover, smoking is a risk factor for both cardiovascular disease and TAO. In conclusion, visceral involvement is extremely rare and can be considered an atypical manifestation of TAO. The diagnosis of TAO is difficult because of the lack of meaningful diagnostic criteria and the overlap of symptoms with cardiovascular diseases. Thus, coronary TAO needs to be considered in young patients with coronary artery disease and no other CV risk factors besides smoking.

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References

1. Becit N, Unlü Y, Koçak H, Ceviz M. Involvement of the coronary artery in a patient with thromboangiitis obliterans. A case report. *Heart Vessel* 2002; 16: 201-3.
2. Olin JW. Thromboangiitis obliterans (Buerger's disease). *N Engl J Med* 2000; 343: 864-9.
3. Nielubowicz J, Rosnowski A, Pruszynski B, Przetakiewicz Z, Potemkowski A. Natural history of Buerger's disease. *J Cardiovasc Surg* 1980; 21: 529-40.
4. Adar R, Papa MZ, Halpern Z, et al. Cellular sensitivity to collagen in thromboangiitis obliterans. *N Engl J Med* 1983; 308: 1113-16.
5. Hagen B, Lohse S. Clinical and radiologic aspects of Buerger's disease. *Cardiovasc Intervent Radiol* 1984; 7: 283-93.
6. Dehaine-Bamberger N, Amar R, Touboul C, Emmerich J, Fiessinger JN. Buerger disease, clinical prognostic aspects. 83 cases. *Presse Med* 1993; 22: 945-8.
7. Shionoya S, Ban I, Nakata Y, Matsubara J, Shinjo K. Diagnosis, pathology and treatment of Buerger's disease. *Surgery* 1974; 75: 695-700.
8. Horton BT. The outlook in thromboangiitis obliterans. *JAMA* 1988; 111: 2184-9.
9. Olin JW, Lie JT. Thromboangiitis obliterans (Buerger's disease). In: Loscalzo J, Creager MA, Dzau VJ, eds. Vascular Medicine. 2nd edn. Boston: Little, Brown, 1996: 1033-49.
10. Papa MZ, Rabi I, Adar R. A point scoring system for the clinical diagnosis of Buerger's disease. Eur J Vasc Endovasc Surg 1996; 11: 335-9.
11. Fiessinger JN. Buerger's disease or thromboangiitis obliterans. In: Tooke JE, Lowe GD, eds. A Textbook of Vascular Medicine. London/Sydney/Auckland: Arnold, 1996: 275-86.
12. Kakihana A, Ishida A, Miyagi M, et al. Improvement of cardiac function after granulocyte-colony stimulating factor-mobilized peripheral blood mononuclear cell implantation in a patient with non-ischemic dilated cardiomyopathy associated with thromboangiitis obliterans. *Intern Med* 2009; 48: 1003-7.
13. Hsu PC, Lin TH, Su HM, Voon WC, Lai WT, Sheu SH. Frequent accelerated idioventricular rhythm in a young male of Buerger's disease with acute myocardial infarction. *Int J Cardiol* 2008; 127: e64-6.
14. Hong TE, Faxon DP. Coronary artery disease in patients with Buerger's disease. *Rev Cardiovasc Med* 2005; 6: 222-6.
15. Heno P, Fourcade L, N'Guyen DH, et al. Buerger's disease and coronary disease. *Arch Mal Coeur Vaiss* 2000; 93: 1239-42.
16. Harten P, Müller-Huelsbeck S, Regensburger D, Loeffler H. Multiple organ manifestations in thromboangiitis obliterans (Buerger's disease). A case report. *Angiology* 1996; 47: 419-25.
17. Kim KS, Kim YN, Kim KB, Park SK. Acute myocardial infarction in a patient with Buerger's disease. A case report and a review of the literature. *Korean J Intern Med* 1987; 2: 278-81.
18. Ohno H, Matsuda Y, Takashiba K, Hamada Y, Ebihara H, Hyakuna E. Acute myocardial infarction in Buerger's disease. *Am J Cardiol* 1986; 1: 690-1.
19. Donatelli F, Triggiani M, Nascimbene S, et al. Thromboangiitis obliterans of coronary and internal thoracic arteries in a young woman. *J Thorac Cardiovasc Surg* 1970; 113: 800-2.
20. Umami T, Ohno T, Ohkawa Y, Doi H, Sasaki A, Sugiki K. A case of coronary artery bypass grafting in a patient who has a rosary-like coronary lesion with Buerger's disease. *Kyobu Geka* 1999; 2: 55-7.
21. Korsgaard N, Johansen A, Baandrup U. A case of thromboangiitis obliterans affecting coronary, pulmonary, and splenic vessels. Is thromboangiitis obliterans a generalized vascular disease? *Am J Cardiovasc Pathol* 1988; 2: 263-7.
22. Rodriguez-Fernandez J, Rangel A, Chavez E. Myocardial infarction simultaneous with Buerger disease (obliterating thromboangiitis). A case report. *Arch Cardiol Mex* 2002; 72: 306-10.
23. Hoppe B, Lu JT, Thistlewaite P, Yi ES, Mahmud E. Beyond peripheral arteries in Buerger's disease: angiographic considerations in thromboangiitis obliterans. *Catheter Cardiovasc Interv* 2002; 57: 363-6.
24. Mautner GC, Mautner SL, Lin F, Roggin GM, Roberts WC. Amounts of coronary arterial luminal narrowing and composition of the material causing the narrowing in Buerger's disease. *Am J Cardiol* 1993; 71: 486-90.
25. Puéchal X, Fiessinger NJ. Thromboangiitis obliterans or Buerger's disease: challenges for the rheumatologist. *Rheumatology* 2007; 46: 192-9.
26. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. *N Engl J Med* 2005; 352: 1685-5.