Virchows Arch (2000) 436:59–67

ORIGINAL ARTICLE

Atsushi Kurata · Folker E. Franke
Rikuo Machinami · Andreas Schulz

Thromboangiitis obliterans: classic and new morphological features

Received: 26 April 1999 / Accepted: 7 August 1999

Abstract The clinical and pathological concept of thromboangiitis obliterans (TAO, Buerger's disease) is still controversial. While the clinical criteria of TAO are relatively well defined, the etiology is unknown and its diagnosis based on pathology is confusing, since there is no consensus on the precise pathological criteria for TAO. To investigate the morphological features that differentiate TAO from arteriosclerosis obliterans (ASO) or thromboembolism, and to clarify the morphological independence of TAO, we studied 94 amputated specimens of lower extremities, including 31 specimens from patients with a clinical diagnosis of TAO and 31 autopsy specimens as control cases. It was revealed that most of the classic morphological features described by Buerger and others are not helpful when considered independently in the differential diagnosis, except for intact internal elastic lamina. In addition, findings of intimal inflammation, intact media and absence of medial calcification were demonstrated to be common in both TAO and thromboembolism. Statistical analysis in the present study, the most comprehensive thus far, showed that novel findings of onion-like-shaped recanalizing vessels in the occluded arteries, adventitial fibrosis without medial fibrosis, swelling of the endothelium of the vasa vasorum and edema beneath the external elastic lamina were characteristic of TAO and would be helpful in a differential diagnosis. When a combination of these morphological features is present, diagnosis of a presumed overlap of TAO and ASO in the same site of the vessel concerned is possible. Furthermore, comparison of statistical evaluations based on morphological features performed in various diagnostic groups implies that the clinical diagnosis of TAO is currently underestimated because the results of the analysis of morphological features of specimens in which TAO was suspected or specimens selected on the basis of a broad and nonspecific definition of TAO were surprisingly similar to the results in strictly defined TAO cases. Our findings suggest that injury and regeneration of minute vessels such as recanalizing vessels and vasa vasorum play a part in the pathogenesis of TAO.

Key words Thromboangiitis obliterans · Atherosclerosis · Thromboembolism · Arteritis · Pathology

A. Kurata (✉) · R. Machinami
Department of Pathology, The University of Tokyo,
Faculty of Medicine, Hongo 7-3-1, Bunkyo-ku,
Tokyo 113–0033, Japan
e-mail: akurata-tky@umin.u-tokyo.ac.jp
Tel.: +81-3-3815-5411 (35235) (office),
+81-3-3812-2111 (23340) (secretary)
Fax: +81-3-3815-8379

F.E. Franke · A. Schulz
Department of Pathology, Justus-Liebig University of Giessen,
Giessen, Germany

Introduction

Thromboangiitis obliterans (TAO, Buerger's disease) is an uncommon, but not extremely rare, disease. It occurs more often in Asian than in Western countries. Since the first detailed morphological description by Buerger in 1908 [7], there have been a multitude of clinical and pathological communications about TAO. Nevertheless, its etiology remains obscure [9, 25, 33, 34, 40, 42]. It occurs more often in young males and cigarette smokers, and the lower extremities are the main target of this vaso-occluding disease [9, 10, 24, 25, 30, 40, 42]. To reduce or diminish the ischemic effects of TAO, several different therapeutic approaches have been undertaken [13, 33, 40, 41].

In contrast to clinical trials, there has been little progress in defining the histological features of TAO. Recently, there have been few reports presenting morphological data on TAO (Table 1). In particular, features that would be useful in diagnosis, and especially any that might help in differentiating arteriosclerosis obliterans (ASO) from TAO, are lacking. Furthermore, it remains unsettled whether TAO and thrombotic disorders, such as systemic or peripheral thrombosis and embolism, are separate entities [3, 15, 23, 27, 43, 44].

Table 1 Morphological findings reported on thromboangiitis obliterans (TAO). Survey of English medical literature of reports describing morphology of more than 5 cases (*IEL* internal elastic lamina, *NEA* newly formed elastic lamina around recanalizing vessels, *NEP* newly formed elastic lamina paralleling IEL, – no comment, *ns* nonspecific, *ct* not specific but characteristic of TAO, *st* specific to TAO, *ca* characteristic of ASO)

Reference	Year	Collective: specimens/ patients[a]	Specimen: amputation/ biopsy/control[b]	Diagnosis: TAO specimens/ TAO patients[a]	Findings: giant cells[c]	Abundant								
						NEA	NEP		Inflamed intima	Intact IEL	Intact media	vasa vasorum	Inflamed adventitia	Fibrotic adventitia	Venous lesions
7	1908	11/?	11/0/0	11/?	ct	ct	ca	ct	ct	ct?	–	ct	ct	ct	ct
15	1958	15/10	15/0/0	15/10	ns	–	–	ns	–	–	–	ns	ns	ns	–
44	1960	119/92	39/14/66	<35/<18	ns	–	–	ns	ns	ns	ns	–	ns	ns	ns
27	1962	33	31/2/0	33/10	ct	–	–	–	ct	ct	ct	–	–	–	ct
45	1969	82/37	0/82/0	82/37	ct	–	–	ct	ct	ct	ct	ct	ct	ct	ct
38	1973	18/?	18/0/0	18/?	–	–	–	st?	ct	ct	–	st?	st	st	st?
35	1974	60/15	60/0/0	60/15	–	–	–	ns	–	–	–	ct?	–	–	ct?
34	1974	25/25	25/0/0	25/25	–	ct	–	ct	ct	ct	ct	ct	ct	ct	ct
23	1976	115/?	115/0/0	25/?	ns	–	–	ns	ns	ns	ns	ns	ns	ns	ns
24	1987	12/?	9/3/0	12/?	st?	–	–	ct	ct?	ct?	ct	–	ct?	ct	ct
(present data)	1999	125/110	94/0/31	31/26	–	ns	ns	ns	ct	ns	ns	ns	ns	ns	ns

[a] More than one amputation or biopsy of the same patient were sometimes analyzed
[b] Including autopsies
[c] Only in acute stage

Currently, TAO is most often diagnosed clinically after the exclusion of other arterial diseases and of atherosclerotic risk factors other than smoking, since pathological findings are regarded as imprecise [9, 40]. On the other hand, documentation based on histological findings of atypical TAO, e.g., that affecting women [11, 14], visceral or cerebral blood vessels [11, 16, 37], a diabetic patient [14] and nonsmokers [11, 14] has been increasing. Therefore, there is a question of whether there is room for over- or underdiagnosis. The long-term prognosis and survival rate of TAO have been reported to be more favorable than those of ASO [25, 29, 32]. Taking these factors into consideration, there is a need for distinct histopathological criteria for the diagnosis of TAO.

Materials and methods

Patients, tissues and slide preparations

We studied 94 amputated specimens of lower extremities from 79 patients (11 women) aged 20–88 years (mean 57). Patients underwent amputation owing to gangrene in Tokyo University Hospital from 1970 to 1986 (59 specimens), Toranomon Hospital in Tokyo from 1976 to 1983 (26 specimens) or Kanto Teisin Hospital in Tokyo from 1982 to 1996 (9 specimens). Amputations were below the thigh, knee, heel and toe in 13, 33, 26, and 22 specimens, respectively. After fixation in 10% formalin, specimens were cut into transverse segments at intervals of 2–3 cm. Representative smaller pieces 0.5 cm thick were embedded in paraffin, and 4-µm tissue sections of the sample were stained with hematoxylin and eosin, elastica–van Gieson, and Masson's trichrome. As control specimens (no gangrene), 31 autopsy specimens taken at Tokyo University from 1996 to 1997 from subjects aged 34–86 years (mean 72) were studied in the same way. All specimens were taken from below the level of the thigh and included popliteal, anterior tibial, posterior tibial and peroneal arteries along with the parallel veins.

Recorded clinical diagnosis

Clinical diagnoses causing gangrene in 94 specimens were: TAO 31, ASO 27, chronic arterial occlusion (CAO; no characteristic symptoms of ASO or TAO [21]) 12, diabetes mellitus (DM) 8, thrombus 4, progressive systemic sclerosis (PSS) 4, polyarteritis nodosa (PN) 3, and necrosis 5. The diagnosis was chiefly based on clinical history, signs, laboratory data, and arteriography.

Recorded pathological diagnosis

Pathological diagnoses of 94 amputated lower extremities were: TAO 24, compatible with TAO 7, ASO 32, ASO with angiitis 1, diabetic gangrene 1, thrombosis 4, arteritis 4, compatible with PSS 1, and necrosis 20. The diagnosis was based mainly on the presence or absence of morphological features such as recanalization vessels (REC), alteration of internal elastic lamina (IEL) or media, increase of vasa vasorum and calcification or cholesterol clefts. Diagnoses varied among the 31 autopsy specimens: cancer, 15; heart failure, 5; pneumonia, 2; aortic aneurysm, 2; leukemia, 2; and 1 case each of liver cirrhosis, ASO, PSS, Machado-Joseph disease and Crow-Fukase syndrome.

Re-evaluation of clinical diagnosis

In order to define the cause of gangrene by definite and independent diseases, all available clinical data on 94 specimens were re-

Table 2 Morphological criteria for TAO: specificity of histological findings compared with defined diagnostic groups [*Q* quantity was valued, *D* degree was valued, *NEA* (no. 1), *NEP* (no. 2), *REC* recanalizing vessels (no. 3), *IEL* (no. 6), *EEL* external elastic lamina (no. 10), *ECVV* endothelial cells of vasa vasorum (no. 12), *AF* adventitial fibrosis, *MF* medial fibrosis (no. 15), *ns* nonspecific, *ct* characteristic of TAO, *ca* characteristic of ASO]

Histological findings[a]		Diagnostic groups 1–4:					Estimation of specificity
		1	2	3	4	Total	
No.		TAO 12	Suspected TAO 17	ASO 22	Thromboembolism 12	72	
1	Q: NEA	6/6[b]	7/10	1/21	3/9	18/54	ns
2	Q: NEP	1/11	2/15	14/8	8/4	30/42	ns
3	Q: onion-like shaped REC	8/4	8/9	0/22	1/11	17/55	ct
4	Q: cholesterol clefts	0/12	0/17	8/14	4/8	15/57	ca
5	D: intimal inflammation	10/2	7/10	7/15	8/4	35/37	ns
6	D: intact IEL	5/7	2/15	1/21	1/11	9/63	ct?
7	D: medial calcification	0/12	0/17	8/14	3/9	14/58	ca
8	D: medial fibrosis	1/11	1/16	15/7	8/4	31/41	ns
9	D: medial atrophy	1/11	0/17	13/9	1/11	17/55	ca?
10	D: edema beneath EEL	10/2	7/10	3/19	0/12	20/52	ct?
11	Q: vasa vasorum	10/2	9/8	8/14	5/7	36/36	ns
12	D: swelling of ECVV	7/5	10/7	2/20	0/12	19/53	ct?
13	D: adventitial inflammation	4/8	6/11	3/19	2/10	17/55	ns
14	D: adventitial fibrosis	10/2	10/7	8/14	4/8	34/38	ns
15	D: AF without MF	6/6	4/13	0/22	0/12	10/62	ct
16	D: venous inflammation	5/7	4/13	2/20	0/12	12/60	ns
17	D: venous thrombosis	10/2	10/7	5/17	1/11	28/44	ns

[a] Main ananomical sites in estimating each histological finding are: intima (no. 1–5), internal elastic lamina (no. 6), media (no. 7–10), vasa vasorum (no. 11, 12), adventitia (13–15) and adjacent veins (16, 17)

[b] Case ratio: obviously present / absent or slightly present

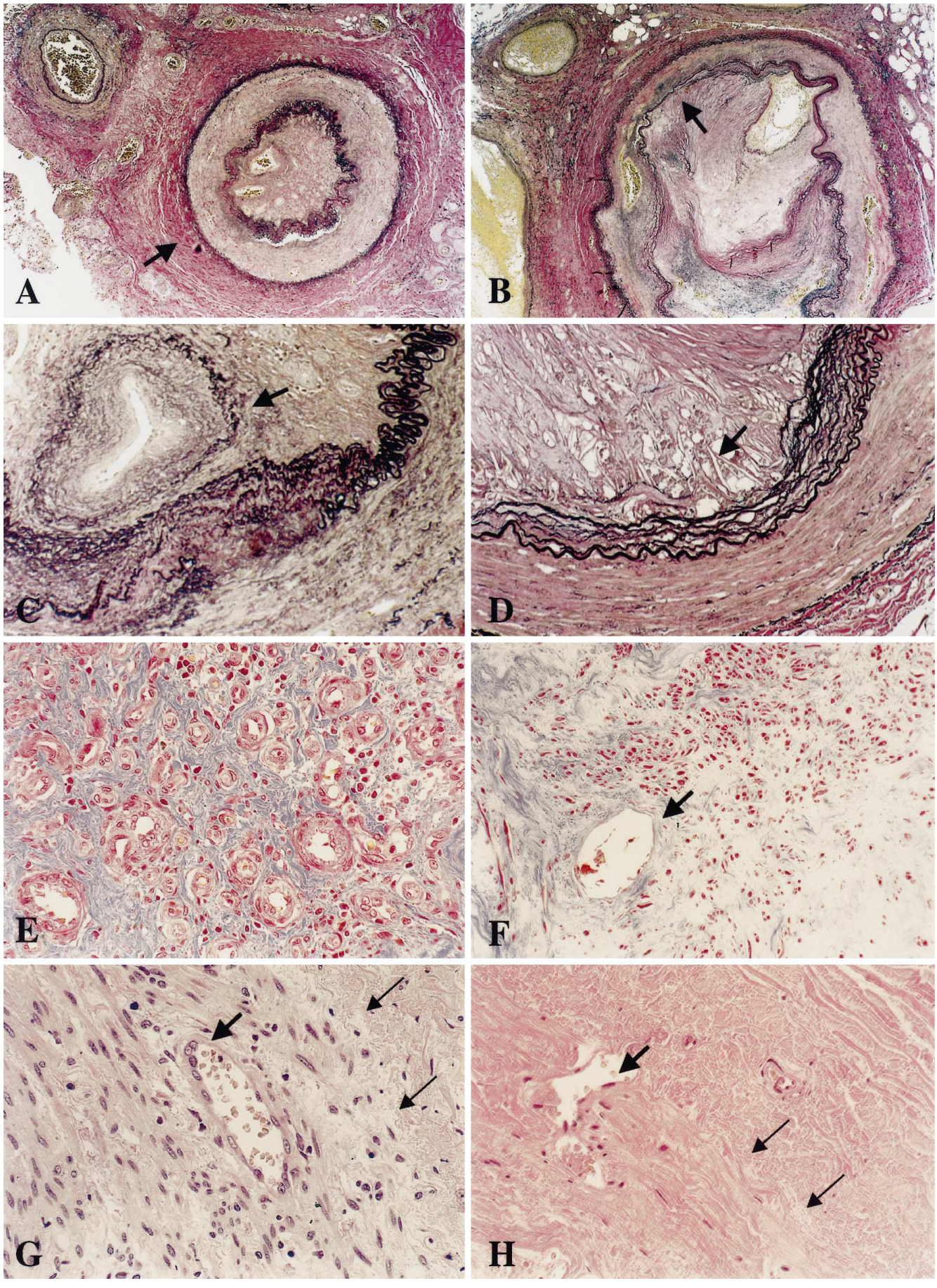
evaluated. Based on these data the specimens were assigned to four diagnostic groups without regard for the original recorded diagnosis. The first group, definite TAO specimens, fulfilled all five of the clinical criteria proposed by Shionoya [39]: (1) smoking habit; (2) onset of symptoms before the age of 50; (3) infrapopliteal arterial occlusion; (4) phlebitis migrans or upper extremity involvement; and (5) absence of atherosclerotic risk factors such as hypertension, hypercholesteremia and DM. The second group, specimens from suspected TAO cases, fulfilled 4 of the above 5 criteria. The third group, definite ASO specimens, fulfilled all of the following three criteria: (1) onset of the symptoms after the age of 50 [17, 40]; (2) absence of phlebitis migrans and upper extremity involvement [23, 29]; and (3) presence of hypertension or hypercholesteremia [17, 22, 23]. The fourth group, thromboembolic cases, included 4 specimens with a clinically diagnosed thrombus and 3 specimens of pathologically confirmed digital cholesterol emboli. All patients in this group had a sudden onset and were confirmed to have atrial fibrillation on electrocardiogram. Five cases among the additional controls were incidentally found to have occluded infrapopliteal arteries in combination with a clinical history of chronic heart failure or systemic embolism. These were included in the fourth group. The numbers of specimens were: group 1: 12, 2: 17, 3: 22, 4: 12 (Table 2).

Re-evaluation of pathological features

One to three representative preparations for each specimen, mostly those in which the most severely narrowed arteries were included, were analyzed with regard to the following morphological details. If necessary, additional sections were examined. The expression of each morphological feature was scored from 0 to 3 (0: absent; 1: slightly present; 2: obviously present; 3: present over a wide range). Examples of features with score values of 2 or 3 are given in Figs. 1 and 2. In the intima, quantity of newly formed elastic lamina around REC (NEA) (Fig. 1A, C), newly formed elastic lamina paralleling IEL (NEP) (Figs. 1B–D), onion-like-shaped REC showing stratification of endothelium or basement membrane (Fig. 1E), cholesterol clefts (Fig. 1D) and degree of inflammation (Fig. 1E) were assigned values. Degree of bend (intactness) of IEL (Figs. 1A, 2A and 2B) was assigned a value. In the media, degree of calcification (Fig. 2G), fibrosis (Fig. 1B), atrophy caused by intimal thickening (Fig. 1B) and edema beneath external elastic lamina (Figs. 1G, 2A) were assigned values, as were the quantity of vasa vasorum (Fig. 1A) and degree of swelling of endothelial cells of vasa vasorum (Fig. 1G). In the adventitia, values were given to the degree of inflammation (Fig. 2A) and fibrosis (Figs. 1A, B, 2A). The degree of adventitial fibrosis without medial fibrosis (Figs. 1A, 2A) was also valued. Finally, values were assigned to the degree of inflammation and thrombosis of adjacent veins (Fig. 2A). [7, 10, 26, 38]. For simplified comparison of the specimen ratios shown in Table 2, data values of the initial scoring were merged as follows: scores of 0 and 1 were altered to 0 (no or slight expression of features), and scores of 2 and 3 were altered to 1 (obvious expression of features).

Statistical analysis

Statistical analysis, including Chi-square test, Spearman's rank correlation and logistic regression models, was performed with the SPSS software program using the above scores (0–3). Initially, this analysis was performed for the diagnostic groups established as described above. Furthermore, a possible bias in histology that might otherwise have been caused by an amputation below the anatomical position of the occluded artery (sample error) was avoided by excluding such samples. For the final statistical analysis, only the 53 specimens (groups 1'–4') that showed either complete occlusion or at least 70% stenosis with the presence of recanalizing vessels of arteries were included. The number of specimens in these groups were: group 1': 12; 2': 9; 3': 14; and 4': 12 (Table 3). In addition, the same analysis was performed for all specimens based on the original recorded diagnosis. To investigate age-related influences, specimens in each of these four groups were divided in half into those from younger and from older patients, and the same analysis was performed for the sum of specimens from younger patients versus those from older patients in each of the four groups.


A
B
C
D
E
F
G
H

Results

TAO patients in this retrospective study were mainly those at the secondary (intermediate) and tertiary (chronic) stages [7]. Multinucleated giant cells within the occluded vascular lumen, which Buerger regarded as characteristic of the first (acute) stage of TAO [7, 8], were found in only one specimen within conspicuous microabscesses of the vascular intima (Fig. 2E). More frequently found observations were giant cells or giant cell-like phenomena clearly not associated with TAO, which indicated degeneration of endothelial cells or other pathological alterations of the vascular wall (Fig. 2F). Also in ASO, an osteoclastic giant cell was found adjacent to ossification of the media (Fig. 2G).

Table 2 provides a survey of various dichotomized histological features and their relation to certain diagnostic groups. Such features as the presence of onion-like-shaped REC and adventitial fibrosis without medial fibrosis appear to be typical findings exclusively in TAO or suspected TAO specimens compared with those of ASO and thromboembolism. Intact IEL, edema beneath external elastic lamina and swelling of endothelial cells of the vasa vasorum were rarely present in specimens affected by ASO and thromboembolism. Intact IEL is known to be characteristic of TAO, but the latter two features are novel findings in this disorder. In contrast, cholesterol clefts and medial calcification were not found in TAO or suspected TAO specimens. They were regarded as characteristic of ASO, although some specimens of thromboembolism had findings in common with ASO. Medial atrophy was a typical finding in ASO, but absence of this feature was common in TAO and thromboembolism. Other features were estimated as nonspecific, because they were common in all diagnostic groups.

◀ **Fig. 1A–H** Photomicrographs of thromboangiitis obliterans (*TAO*: **A**, **C**, **E**, **G**) and arteriosclerosis obliterans (*ASO*: **B**, **D**, **F**, **H**). **A** Prominent adventitial fibrosis without medial fibrosis, abundant vasa vasorum in the media and numerous recanalizing vessels (*REC*) in the intima are visualized. Internal elastic lamina (*IEL*) is preserved. No medial atrophy is seen (*arrow*). Elastica–van Gieson, ×40 **B** Obvious adventitial fibrosis with medial fibrosis (*arrow*) and a moderate quantity of vasa vasorum and REC are visualized. Newly formed elastic lamina paralleling IEL (*NEP*) is widely present on the lower side. Bend of IEL is not preserved. Media is compressed and atrophic (*arrow*). Elastica–van Gieson, ×20 **C** Conspicuous newly formed elastic lamina around recanalizing vessels (*NEA*) (*arrow*) and obvious NEP are shown. Elastica–van Gieson, ×200 **D** Obvious NEP and abundant cholesterol clefts (*arrow*) are shown. Elastica–van Gieson, ×200 **E** Numerous onion-shaped REC with marked inflammation are widely noticeable in the intima. Masson's trichrome, ×200 **F** Single thin layer of endothelium of REC with slight inflammation is present in the intima. Masson's trichrome, ×200 **G** Marked edema beneath the external elastic lamina (*thin arrows*) and swelling of endothelial cells of vasa vasorum (*thick arrow*) in the media are observed. Hematoxylin and eosin, ×200 **H** No edema beneath the external elastic lamina (*thin arrows*) and no swelling of endothelial cells of vasa vasorum (*thick arrow*) in the media are shown. Hematoxylin and eosin, ×200

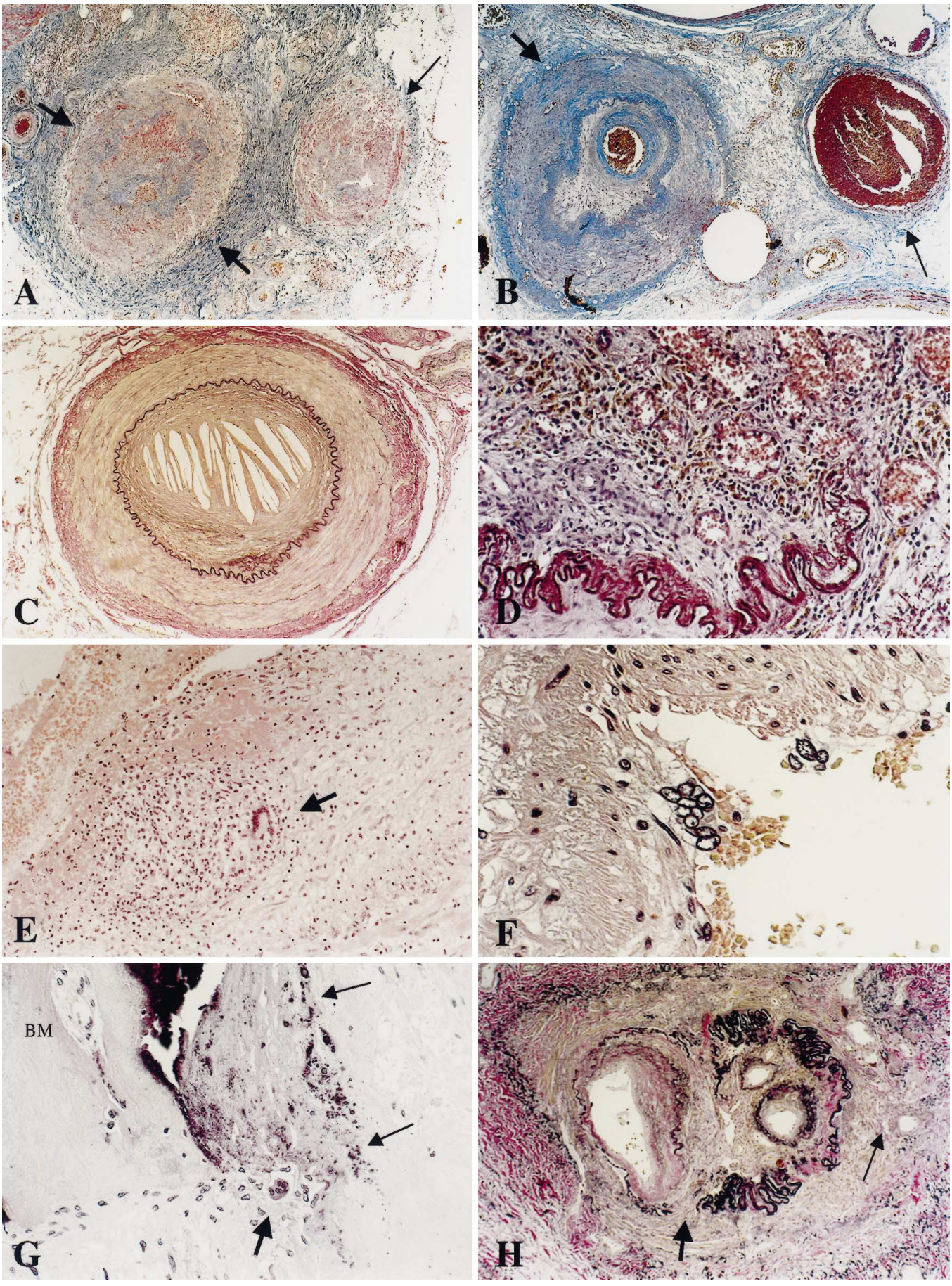
Statistical analysis using Spearman's rank correlation verified these findings even for the more strictly defined groups 1'–4' and the more broadly defined specimens based on clinical diagnosis (Table 3). Comparison of the analysis of definite TAO versus ASO with that of definite TAO versus thromboembolism showed that the degrees of intimal inflammation, medial calcification and medial atrophy have less importance for differentiating TAO from thrombosis than from ASO, which indicates that both presence and absence of these features are common in both TAO and thromboembolism. Results of analysis of specimens from patients suspected of having TAO paralleled those of analysis of definite TAO specimens when they were differentiated from specimens of ASO or thromboembolism. Differentiation of the more broadly defined clinically diagnosed TAO versus ASO and clinically diagnosed TAO+CAO versus all others, including autopsy controls, showed almost the same results as with the more strictly defined groups. Age-related influences on the vascular morphology had no relevance, as there were no significant differences between specimens from younger and older patients in groups 1'–4' (n=26, mean age 55.1 years vs n=27, mean age 65.9 years).

Logistic regression analysis regarding group 1' versus groups 3'+4' indicated that edema beneath the external elastic lamina and swelling of endothelial cells of the vasa vasorum were most important as the basis for a diagnosis of TAO. Depending on only these two factors, discrimination of group 1' specimens from those in groups 3'+4' was possible with 97% accuracy.

When the above criteria were applied to all specimens, a peculiar finding was noted in the bifurcation of the infrapopliteal artery in an autopsy control obtained from a 70-year-old man who had died of hepatocellular carcinoma. In this patient heavy smoking was recorded, but no gangrene and no history of thromboembolism. In fact, morphology within the same site of the vessel (Fig. 2H) suggests that both latency of TAO and complications of progressive atherosclerosis may occur concomitantly.

Discussion

This study shows that the clinical syndrome of TAO is associated with specific morphological changes of the affected vessels. Indeed, since the first description by Buerger it has been questioned whether or not TAO exists. However, no significant progress has been made in establishing the specific morphology for this condition. Although the clinical features of the syndrome have been established [9, 24, 25, 39, 40], pathological findings are generally believed not to be very helpful for a differential diagnosis, at least in the secondary and tertiary stages of TAO [1, 15, 23–25, 39, 40]. Even in its first stage, TAO has been reported to be morphologically indistinguishable from ASO or thrombotic disorders [15, 23, 30, 43, 44]. However, this opinion contrasts with the lack of systematic clinical and histopath-


A
B
C
D
E
F
BM
G
H

ological studies with the use of defined tissue samples and analytical methods. As the recorded pathological diagnosis has almost always paralleled the clinical diagnosis in routine work, pathologists seem to be influenced by the clinical diagnosis [3]. This reflects the paucity of precise morphological definition of what is called TAO [1, 15].

The most important differential diagnoses of TAO are ASO and thromboembolism. This would exclude certain other vascular diseases with possible arterial occlusion, such as Takayasu's arteritis, which affects the more proximal elastic arteries with destruction of medial elastic fibers; polyarteritis nodosa, generally manifested by fibrinoid necrosis in the vessel walls [27]; popliteal artery entrapment syndrome, in which arteriography shows medial deviation of popliteal arteries [19, 20], and PSS, Beçet's disease and inflammatory vascular diseases accompanied by immunological abnormalities. Although there may be some specimens with association of ASO with thromboembolism in the thromboembolic group in our data, it is difficult to draw a clear separation between these two diseases, because generally thrombosis tends to be superimposed on atherosclerosis [23].

Which features are reliably characteristic of TAO, and which can be considered newly described by this review? Here, we have confirmed that most of the classic morphological features described by Buerger and others tend to be observed more in TAO than in the other diseases. However, their obvious expression was often observed in ASO and thromboembolism, except for the presence of intact IEL. Thus, the presence of NEA, intimal inflammation, abundant vasa vasorum, adventitial inflammation and fibrosis, and venous inflammation and thrombosis are not always useful individually in the differential diagnosis. In addition, statistical evaluation demonstrated that the presence of intimal inflammation, medial calcification and medial atrophy were not significant in the differentiation of TAO from thrombosis, although they were significant in TAO versus ASO. This suggests that TAO and thromboembolism are common insofar as thrombus and inflammation occur in the inner circle of the lumen and simultaneously without strongly oppressing the media, as noted by McKusick et al. [27], while atherosclerosis occurs and usually progresses asymmetrically from one side of the lumen as influenced by blood flow [17]. Our most striking finding was that the occurrence of onion-like-shaped recanalizing vessels and of adventitial fibrosis without medial fibrosis are virtually specific morphological findings of TAO, although these features may be observed in other diseases only to a slight degree. Because of these findings, along with other features, especially the presence of swelling of endothelial cells of the vasa vasorum and prominent edema beneath the external elastic lamina, pathologists can rely on the quite unique histological appearance of vessels affected by TAO [26].

Currently, owing to improvements in clinical treatment, amputation of the affected limb may result almost exclusively in the secondary and tertiary stages of TAO [39]. This differs from the era of Buerger, when patients sometimes chose amputation on account of pain, and not of gangrene [7, 8]. We did not conclude whether multinucleated giant cells within the occluded vascular lumen are characteristic of TAO, but pathologists should take care to differentiate these from other ambiguous giant cells, for example in the degeneration of endothelial cells or osteoclastic giant cells. However, although the pathological presentation of TAO changes in its secondary and tertiary stages, the difference between TAO and ASO or thromboembolism is definable through the use of the combination of some of the morphological features presented in this study. Depending on our morphological criteria, both latency of TAO and the complication of progressive atherosclerosis in the same site of the artery can be diagnosed. Moreover, our statistical data on true TAO cases were surprisingly similar to those that include the broader clinical diagnosis of CAO (Table 3), suggesting that TAO may be clinically underdiagnosed.

Concerning the etiology and pathogenesis of TAO, it has been disputed whether the primary lesion is inflammation [8, 19, 35] or thrombosis [15, 23, 27, 45]. More recent findings of an increased cellular immune response to collagen types I and III, increased incidence of the HLA-A9 and HLA-B5 antigens, and elevated anti-elastin titers in TAO patients, however, point to an inflammatory and immunological genesis of this smoking-related vascular disorder [2, 5, 18, 28]. This concept of a primary inflammatory lesion is supported by our study. The findings of onion-like-shaped recanalizing vessels caused by the excessive formation of vascular smooth muscle cells [A. Kurata, unpublished data], swelling of endothelial cells and chronic inflammation with marked edema beneath the external elastic lamina indicate that minute vessels such as recanalizing vessels and vasa vasorum are involved in the

◀ **Fig. 2A–H** Photomicrographs of TAO (**A**, **E**, **F**), old thrombosis (**B**), cholesterol emboli (**C**), acute thrombosis (**D**), ASO (**G**) and presumably overlapping between TAO and ASO in an autopsy specimen (**H**). **A** Obvious adventitial fibrosis without medial fibrosis, marked edema beneath the external elastic lamina (*thick arrows*) and venous thrombosis with inflammation (*thin arrow*) are shown. Adventitial inflammation is obvious in the upper side. IEL and media are preserved. Masson's trichrome, ×40 **B** No adventitial fibrosis with slight medial fibrosis (*thick arrow*), no edema beneath the external elastic lamina and no venous thrombosis or inflammation (*thin arrow*) are shown. IEL and media are preserved. Masson's trichrome, ×200 **C** Vasa vasorum and REC are scanty. Slight quantity of NEP is observed. IEL is slightly compressed circularly. Media is preserved. Elastica–van Gieson, ×100 **D** Marked intimal inflammation with a single thin layer of endothelium of REC is observed. Hematoxylin and eosin, ×200 **E** Multinucleated giant cell (*arrow*) within micro-abscess of stenotic vascular lumen is present. Hematoxylin and eosin, ×100 **F** Degenerated endothelial cells in vascular lumen resemble multinucleated giant cells. Hematoxylin and eosin, ×400 **G** Calcification (*thin arrows*) and ossification with formation of bone marrow (*BM*) of media are found. Osteoclastic giant cell is present (*thick arrow*). Hematoxylin and eosin, ×200 **H** In the right side of the artery, NEA is prominent, IEL and media are preserved, and edema and swelling of endothelial cells of vasa vasorum are observed (*thin arrow*), suggesting TAO. In the left side of the artery NEP is prominent, IEL is compressed and fragmented (*thick arrow*), media is partially thinned, and neither edema nor swelling of endothelial cells of vasa vasorum is observed, suggesting atherosclerosis. Elastica–van Gieson, ×100

Table 3 Morphological criteria in the differential diagnosis of TAO (Spearman's rank correlation of histological findings to re-evaluated and clinically established diagnosis). Each factor in each evaluation was marked according to correlation coefficient as three arrows (rho>0.6, $P<0.05$), two arrows (rho: 0.4–0.6, $P<0.05$), 1 arrow (rho<0.4, $P<0.05$) and lateral arrows ($P>0.05$). Upper and rightward arrows indicate correlation with upper rows, while lower and leftward arrows indicate correlation with lower rows [↑-↑-↑- rho >0.6, $P<0.05$, ↑-↑- 0.4<rho <0.6, p<0.05, ↑- rho <0.4, $P<0.05$, →® rho <0.4, $P>0.05$. (correlation with upper row – TAO); ↓⁻↓⁻↓⁻ rho >0.6, $P<0.05$, ↓⁻↓⁻ 0.4<rho <0.6, $P<0.05$, ↓⁻ rho <0.4, $P<0.05$, ←¬ rho<0.4, $P>0.05$ (correlation with lower row – other diseases)]

Histological findings[a]	Diagnostic groups 1'–4'								Clinical diagnosis				Relative age	
	1' – definite TAO *n*=12 versus				2' – suspected TAO *n*=9 versus				TAO *n*=31 versus		TAO+CAO *n*=43 versus		All younger 1'–4' *n*=26 versus	
	3' Definite ASO		4' Thromboembolism		3' Definite ASO		4' Thromboembolism		ASO		All others Including autopsy control		All older 1'–4'	
No.[b]	14		12		14		12		27		82		27	
1 Q: NEA	→®	*P*=0.036	→®	*P*=0.218	↑—↑-	*P*=0.018	→®	*P*=0.127	↑—	*P*=0.009	↑-	*P*<0.001	←¬	*P*=0.559
2 Q: NEP	↓⁻↓⁻↓⁻	*P*<0.001	↓⁻↓⁻↓⁻	*P*<0.001	↓⁻↓⁻↓⁻	*P*<0.001	↓⁻↓⁻	*P*=0.006	↓⁻↓⁻	*P*<0.001	↓⁻↓⁻	*P*<0001	←¬	*P*=0.157
3 Q: onion-like shaped REC	↑-↑-↑-	*P*<0.,001	↑-↑-↑-	*P*<0.001	↑-↑-↑-	*P*<0.001	↑-↑-↑-	*P*<0.001	↑-↑-↑-	*P*<0.001	↑-↑-↑-	*P*<0001	←¬	*P*=0.775
4 Q: cholesterol clefts	↓⁻↓⁻	*P*=0.007	↓⁻↓⁻	*P*=0.041	↓⁻↓⁻	*P*=0.020	←¬	*P*=0.077	↓⁻	*P*=0.019	↓⁻	*P*=0.005	→®	*P*=0.293
5 D: intimal inflammation	↑-↑-	*P*=0.009	→®	*P*=0.219	→®	*P*=0.952	←¬	*P*=0.312	↑-↑-	*P*<0.001	↑-	*P*=0.007	→®	*P*=0.444
6 D: intact IEL	↑-↑-↑-	*P*<0.001	↑-↑-	*P*=0.026	↑-↑-↑-	*P*<0.001	→®	*P*=0.169	↑-↑-	*P*<0.001	↑-↑-	*P*<0.001	←¬	*P*=0.539
7 D: medial calcification	↓⁻↓⁻	*P*=0.023	←¬	*P*=0.090	←¬	*P*=0.050	←¬	*P*=0.144	↓⁻	*P*=0.003	↓⁻	*P*<0.001	→®	*P*=0.488
8 D: medial fibrosis	↓⁻↓⁻↓⁻	*P*<0.001	↓⁻↓⁻↓⁻	*P*=0.002	↓⁻↓⁻↓⁻	*P*<0.001	↓⁻↓⁻↓⁻	*P*=0.003	↓⁻↓⁻↓⁻	*P*<0.001	↓⁻↓⁻	*P*<0.001	←¬	*P*=0.684
9 D: medial atrophy	↓⁻↓⁻↓⁻	*P*<0.001	←¬	*P*=0.118	↓⁻↓⁻↓⁻	*P*<0.001	↓⁻↓⁻	*P*=0.018	↓⁻↓⁻	*P*<0.001	↓⁻	*P*<0.001	←¬	*P*=0.916
10 D: edema beneath EEL	↑-↑-↑-	*P*<0.001	↑-↑-↑-	*P*<0.001	↑-↑-	*P*=0.019	↑-↑-	*P*=0.009	↑-↑-	*P*<0.001	↑-↑-	*P*<0.001	←¬	*P*=0.604
11 Q: vasa vasorum	→®	*P*=0.101	→®	*P*=0.103	→®	*P*=0.106	→®	*P*=0.116	↑-	*P*=0.002	↑-↑-	*P*<0.001	←¬	*P*=0.359
12 D: swelling of ECVV	↑-↑-↑-	*P*<0.001	↑-↑-↑-	*P*<0.001	↑-↑-↑-	*P*<0.001	↑-↑-↑-	*P*<0.001	↑-↑-↑-	*P*<0.001	↑-↑-	*P*<0.001	→®	*P*=0.591
13 D: adventitial inflammation	→®	*P*=0.129	→®	*P*=0.196	→®	*P*=0.323	→®	*P*=0.434	↑-	*P*=0.014	↑-	*P*=0.001	→®	*P*=0.822
14 D: adventitial fibrosis	↑-↑-	*P*=0.034	↑-↑-	*P*=0.005	↑-↑-	*P*=0.018	↑-↑-↑-	*P*=0.002	↑-	*P*=0.025	↑-	*P*<0.001	←¬	*P*=0.654
15 D: AF without MF	↑-↑-↑-	*P*<0.001	↑-↑-↑-	*P*<0.001	↑-↑-↑-	*P*<0.001	↑-↑-↑-	*P*<0.001	↑-↑-↑-	*P*<0.001	↑-↑-↑-	*P*<0.001	→®	*P*=0.925
16 D: venous inflammation	↑-↑-	*P*=0.008	↑-↑-↑-	*P*=0.001	↑-↑-	*P*=0.034	↑-↑-↑-	*P*=0.001	↑-	*P*=0.003	↑-	*P*=0.002	←¬	*P*=0.841
17 D: venous thrombosis	↑-↑-	*P*=0.002	↑-↑-↑-	*P*<0.001	→®	*P*=0.062	↑-↑-↑-	*P*=0.002	↑-↑-	*P*=0.001	↑-	*P*<0.001	←¬	*P*=0.227

[a] Main ananomical sites in estimating each histological finding are: intima (nos. 1–5); internal elastic lamina (nos. 6); media (nos. 7–10); vasa vasorum (nos. 11, 12); adventitia (nos. 13–15); and adjacent veins (nos. 16, 17)

[b] NEA (no. 1); NEP (no. 2); REC (no. 3); IEL (no. 6); EEL (no. 10); ECVV (no. 12); AF, MF (no. 15)

development of TAO. Thus, we support Majewski et al. in their assertion that injury of the microcirculation may be involved in the pathogenesis of TAO [26]. In addition, Eichhorn et al. have recently reported that anti-endothelial cell antibodies are related to TAO activity [12]. Arterial thrombosis seems to be secondary, caused by ischemic changes progressing from the vascular adventitia towards the intima [35]. In our specimens, the finding of adventitial fibrosis without medial fibrosis was noted exclusively in TAO. Interestingly, it has been demonstrated that the obstruction or elimination of adventitial vasa vasorum brings about arterial luminal occlusion in experimental animal models [4, 6, 31]. As the occlusion of vasa vasorum is not believed to be relevant to atherogenesis [36], this may rather have an important role in TAO. Whether occlusion or vaso-spasm of vasa vasorum may actually occur or may be an initial event at the onset of TAO, however, is unclear and remains to be elucidated.

References

1. Adar R (1974) Buerger's disease – the need for diagnostic criteria. Surgery 76:848
2. Adar R, Papa MZ, Halpern Z, Mozes M, Shoshan S, Sofer B, Zinger H, Dayan M, Mozes E (1983) Cellular sensitivity to collagen in thromboangiitis obliterans. N Engl J Med 308: 1113–1116
3. Annotation: Does Buerger's disease exist? (1960) Lancet II:969
4. Barker SG, Beesley JE, Baskerville PA, Martin JF (1995) The influence of the adventitia on the presence of smooth muscle cells and macrophages in the arterial intima. Eur J Vasc Endovasc Surg 9:222–227
5. Berlit P, Kessler C, Reuther R, Krause KH (1984) New aspects of thromboangiitis obliterans (von Winiwarter-Buerger's disease). Eur Neurol 23:394–399
6. Booth RFG, Martin JF, Honey AC, Hassall DG, Beesley JE, Moncada S (1989) Rapid development of atherosclerotic lesions in the rabbit carotid artery induced by perivascular manipulation. Atherosclerosis 76:257–268
7. Buerger L (1908) Thromboangiitis obliterans: a study of the vascular lesions leading to presenile spontanous gangrene. Am J Med Sci 136:567–580
8. Buerger L (1920) The pathology of thromboangiitis obliterans. Med Rec 97:431–437
9. Cutler DA, Runge MS (1995) 86 years of Buerger's disease – what have we learned? Am J Med Sci 309:74–75
10. Dieble JH (1967) The pathology of limb ischemia. In: Cameron R, Wright GP (eds) Pathological monographs, Edinburgh London, pp 79–96
11. Donatelli F, Triggiani M, Nascimbene S, Basso C, Benussi S, Chierchia SL, Thiene G, Grossi A (1997) Thromboangiitis obliterans of coronary and internal thoracic arteries in a young woman. J Thorac Cardiovasc Surg 113:800–802
12. Eichhorn J, Sima D, Lindschau C, Turowski A, Schmidt H, Schneider W, Haller H, Luft FC (1998) Antiendothelial cell antibodies in thromboangiitis obliterans. Am J Med Sci 315:17–23
13. Fiessinger JN, Schäfer M (1990) Trial of iloprost versus aspirin treatment for critical limb ischemia of thromboangiitis obliterans. Lancet 335:555–557
14. Fujii Y, Ohmura Y, Takeuchi R, Morimoto S, Uchida H, Hayashi K, Sano S (1996) Buerger's disease in a middle-aged woman with diabetes mellitus. A case report. Angiology 47: 97–102
15. Gore I, Burrows S (1958) A reconsideration of the pathogenesis of Buerger's disease. Am J Clin Pathol 29:319–330
16. Harten P, Muller-Huelsbeck S, Regensburger D, Loeffler H (1996) Multiple organ manifestations in thromboangiitis obliterans (Buerger's disease). A case report. Angiology 47:419–425
17. Hines EA Jr, Barker NW (1940) Arteriosclerosis obliterans. A clinical and pathological study. Am J Med Sci 200:717–730
18. Horsch AK, Brechemier D, Robert L, Horsch S (1977) Anti-elastin antibodies in thrombangiitis obliterans (Winiwarter-Buerger disease). Verh Dtsch Ges Inn Med 83:1758–1761
19. Inada K, Iwashima Y, Okada A, Matsumoto K (1974) Nonatherosclerotic segmental arterial occlusion of the extremity. Arch Surg 108:663–667
20. Insua JA, Young JR, Humphries AW (1970) Popliteal artery entrapment syndrome. Arch Surg 101:771–775
21. Ishikawa K, Kawase S, Mishima Y (1962) Occlusive arterial disease in extremities, with special reference to Buerger's disease. Angiology 13:398–411
22. Juergens JL, Barker NW, Hines EA Jr (1960) Arteriosclerosis obliterans. Circulation 21:188–195
23. Kinare SG, Kher YR, Rao G, Sen PK (1976) Pattern of occlusive peripheral vascular disease in India. (clinicopathological study of 79 cases). Angiology 27:165–180
24. Lie JT (1987) Thromboangiitis obliterans (Buerger's disease) in women. Medicine 66:65–72
25. Lie JT (1989) The rise and fall and resurgence of thromboangiitis obliterans (Buerger's disease). Acta Pathol Jpn 39:153–158
26. Majewski W, Marszalek A, Staniszewiski R, Majewski P, Zapalski S, Biczysko W (1997) Clinical and morphological aspects of Buerger's disease. Int Angiol 16:239–244
27. McKusick VA, Harris WS, Ottesen OE, Goodman RM, Shelley WM, Bloodwell RD (1962) Buerger's disease-a distinct clinical and pathologic entity. JAMA 181:5–12
28. McLoughlin GA, Helsby CR, Evans CC, Chapman DM (1976) Association of HLA-A9 and HLA-B5 with Buerger's disease. Br Med J 2:1165–1166
29. McPherson JR, Juergens JL, Gifford RW Jr (1963) Thromboangiitis obliterans and arteriosclerosis obliterans. Clinical and prognostic differences. Ann Intern Med 59:288–296
30. Milton EE (1966) Coexistence of thromboangiitis obliterans and arteriosclerosis: relationship to smoking. J Am Geriatr 14: 846–858
31. Nakata Y, Shionoya S (1966) Vascular lesions due to obstruction of the vasa vasorum. Nature 212:1258–1259
32. Ohta T, Shionoya S (1988) Fate of the ischemic limb in Buerger's disease. Br J Surg 75:259–262
33. Olin JW, Young JR, Graor RA, Ruschhaupt WF, Bartholomew JR (1990) The changing clinical spectrum of thromboangiitis obliterans (Buerger's disease). Circulation 82 [Suppl 5]:IV3–8
34. Patil SD, Talib VH, Sharma KD (1974) Studies on pathology and pathogenesis of thromboangiitis obliterans. Indian J Pathol Bacteriol 17:20–28
35. Reddi HT (1974) Thromboangiitis obliterans and/or Buerger's disease in south india. A review of 70 cases. Int Surg 59: 555–557
36. Ross R (1993) The pathogenesis of atherosclerosis: a perspective for the 1990s. Nature 362:801–809
37. Sauvaget F, Debray M, Herve de Sigalony JP, Fichelle JM, Farge D, Lemann M, Rouffy J (1996) Colonic ischemia reveals thromboangiitis obliterans (Buerger's disease). Gastroenterology 110:900–903
38. Schenk EA (1973) Pathology of occlusive disease of the lower extremities. Cardiovasc Clin 5:287–310
39. Shionoya S (1983) What is Buerger's disease? World J Surg 7: 544–551
40. Shionoya S (1993) Buerger's disease: diagnosis and management. Cardiovasc Surg 18:207–214
41. Sims JR, Hanson EL (1998) Images in clinical medicine. Thromboangiitis obliterans (Buerger's disease) N Engl J Med 339:672
42. Szuba A, Cooke JP (1998) Thromboangiitis obliterans. An update on Buerger's disease. West J Med 168:255–260
43. Wessler S (1969) Buerger's disease revisited. Surg Clin North Am 49:703–712
44. Wessler S, Ming SC, Gurewich V, Freiman DG (1960) A critical evaluation of thromboangiitis obliterans. The case against Buerger's disease. N Engl J Med 262:1149–1160
45. Williams G (1969) Recent views on Buerger's disease. J Clin Pathol 22:573–578