

# Visceral bed involvement in thromboangiitis obliterans: a systematic review

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**Abstract:** One of the challenges of thromboangiitis obliterans (TAO) management is in the patients whose other vascular beds are involved and it remains a challenge to know whether to pursue invasive procedures or to continue medical treatment for such TAO patients. The aim of this review was to investigate reports of the involvement of the visceral vessels in TAO and the related clinical manifestations, management approaches and outcomes. According to our systematic review, the frequency of published articles, the organs most commonly involved were the gastrointestinal tract, the heart, the central nervous system, the eye, the kidneys, the urogenital system, the mucocutaneous zones, joints, lymphohematopoietic system and the ear. Notably, reports of the involvement of almost all organs have been made in relation to TAO. There were several reports of TAO presentation in other organs before disease diagnosis, in which the involvement of the extremities presented after visceral involvement. The characteristics of the visceral arteries looked like the arteries of the extremities according to angiography or aortography. Also, in autopsies of TAO patients, the vascular involvement of multiple organs has been noted. Moreover, systemic medical treatment could lead to the recovery of the patient from the onset of visceral TAO. This study reveals that TAO may be a systemic disease and patients should be aware of the possible involvement of other organs along with the attendant warning signs. Also, early systemic medical treatment of such patients may lead to better outcomes and reduce the overall mortality rate.

**Keywords:** thromboangiitis obliterans, Buerger's disease, visceral vascular bed, ischemia

## Introduction

Until recently, thromboangiitis obliterans (TAO) had been known as a recurrent, non-atherosclerotic segmental inflammatory and occlusive peripheral vascular disease with unknown etiology that is typically seen only in young, male smokers.<sup>1</sup> The dominant clinical manifestation of TAO is in the extremities and usually in the medium- to small-sized vessels of the lower and upper limbs, which can lead to limb loss.<sup>1</sup> Because of the disease's unknown etiology, no treatment protocol is available for TAO, and management of TAO remains a medical challenge.

Although smoking cessation is known to be an important part of any suggested treatment, merely stopping smoking cannot prevent amputation and limb loss during disease flare-ups.<sup>2</sup> Notably, one of the challenges of TAO management is in the patients whose other vascular beds are involved. For instance, in a TAO patient with coronary artery involvement, it remains a

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challenge to know whether to pursue invasive procedures or to continue medical treatment. In addition, the prevalence of TAO is low in comparison to other peripheral arterial diseases (PADs), even in countries in which TAO is common. Moreover, involvement of the visceral vessels is occasionally seen in TAO, which means that the involvement of other vascular beds is quite rare.

For these reasons, our understating of the involvement of other organs and their clinical manifestations and outcomes is poor. As a result, the aim of this review was to investigate reports of the involvement of the visceral vessels in TAO and the related clinical manifestations, management approaches and outcomes from January 1947 through December 2018.

## Literature search

A systematic search for relevant literature published between January 1, 1947 and December 31, 2018 was performed on the PubMed, Science Direct databases and Google Scholar. The search was done in the English language. The reference lists from the retrieved studies were then hand-searched. Search terms included “thromboangiitis obliterans”, “Buerger’s disease”, “Arthritis”, “Skin”, “Cutaneous”, “Nodular erythema”, “Livedo reticularis”, “Erythromelalgia”, “Purpura”, “Renal”, “Kidney”, “Cardiac”, “Coronary”, “Heart”, “Lung”, “Pulmonary”, “Testis”, “Genital”, “Penis”, “Nervous system”, “Cerebral”, “Ophthalmic”, “Eye”, “Muscle”, “Muscular”, “Hearing”, “Ear”, “Carotid”, “Hematology”, “Anemia”, “Lymphadenopathy”, “Bone”, “Skeleton”, “Stomach”, “Liver”, “Spleen”, “Pancreas”, “Bowel”, “Intestine”, “Mesenteric”, “Celiac” with combinations being searched via Boolean operator.

For data extraction, the indices for the diagnosis of TAO from each article were evaluated. Articles whose angiography characteristics or pathology reports did not quite match TAO diagnosis were excluded from our study. We excluded articles for which the full-text was not in English or for which the full-text was inaccessible. The primary data extraction form included the year of publication, author name(s), number of patients, age, chief complaint, duration of disease, smoking status, disease diagnosis, suggested treatment and treatment outcome, all of which were assessed by the two independent reviewers (F.F. and B.F.).

Our search initially identified 210 studies. We checked for duplicates between databases. The remaining studies were further reduced to 173 after screening of the titles and

abstracts. Finally, after applying the exclusion criteria, the total number of relevant studies was reduced to 83.

## Result

According to our systematic review, 83 articles were included, 78 of which were case reports and 2 of which were case series papers, with the final 3 being original papers. Fifteen articles were published prior to the 1980s, and 68 articles were published after 1980.

According to the frequency of published articles, the organs most commonly involved were (1) the gastrointestinal (GI) tract, (2) the heart, (3) the central nervous system, (4) the eye, (5) the kidneys, (6) the urogenital system, (7) the mucocutaneous zones, (8) joints, (9) lymphohematopoietic system and (10) the ear. The search results for each organ are summarized in the following 10 tables.

## Gastrointestinal tract

The systematic search returned 45 articles related to the gastrointestinal tract. We were not able to access the full text of nine articles published prior to 1985, and four articles were not in English. Therefore, these 13 articles were excluded from our study. In total, we reviewed 32 articles comprising 41 patients that were published between 1947 and 2016 (Table 1). The mean age of the patients was  $41 \pm 8$  years. The mean number of cigarettes smoked daily was  $32 \pm 12$ , and the duration of smoking before mesenteric ischemia was  $22 \pm 8$  years. Only one case was female. In 65% of these cases, TAO diagnosis had occurred approximately 8 years before the mesenteric ischemia. In the remaining cases, TAO was diagnosed at the acute abdomen, and the histology examination of the ischemic bowel confirmed TAO diagnosis. The clinical manifestations of the patients consisted of the onset of diffuse abdominal pain in 44% of the cases, weight loss in 20% of the cases, pain in the right lower abdominal quadrant in 12% of the cases, bloody stool in 10% of the cases, postprandial pain in 8% of the cases and epigastric pain resistant to antiulcer treatment in 6% of the cases.

Amongst the included articles, occlusion of the superior mesenteric artery occurred in 53% of the cases, of the inferior mesenteric artery in 12.5% of the cases, of both the superior and inferior mesenteric arteries in 22% of the cases and of the celiac artery and its branches in 12.5% of

the cases. Notably, the involvement of the bowels was almost segmental.

However, as observed through aortography, corkscrew collaterals and skip lesions were less prominent than those observed in the lower extremities. The histology study of the visceral vessels and microvessels revealed the same characteristics as the peripheral vessels in TAO. The mortality rate of the patients due to mesenteric ischemia was 16%. Approximately 12% of the patients without signs of peritonitis underwent conservative medical treatment, all of whom improved, although one developed onset of mortal mesenteric ischemia two months after receiving a high dosage of corticosteroids. Endovascular treatment failed in 50% of the four patients in whom it was attempted. The outcome of 12% of the patients has not been reported.

## Heart and coronary arteries

According to a systemic search, we found 20 related articles. We could not have access to the full text of an article in 1986 and four articles were not in English. In one article published in 1977, the diagnosis of TAO was very uncertain according to the clinical manifestations and histology report, and there was no angiography report for that case to support TAO diagnosis. As a result, the article was excluded from our study. In total, 14 articles related to the heart or coronary arteries published between 1985 and 2018 were included, comprising 14 patients (Table 2). The mean age of the patients was  $39\pm 10$  years. The mean number of cigarettes smoked daily was  $27\pm 13$  and the duration of smoking before mesenteric ischemia was  $21\pm 14$  years. Only one patient was female. In 66% of the cases, TAO diagnosis was made approximately 12 years before cardiac event, and in 34% of the cases, TAO diagnosis occurred soon after hospitalization due to cardiac event.

The occlusion of the left anterior descending artery (LAD) and its branches, including the diagonal and circumflex arteries, in addition to right coronary artery (RCA), was observed in 35% of the cases. The involvement of only the LAD occurred in 41% of the cases, of only the RCA in 18% of the cases, and of the circumflex artery in 6% of the cases. In 71% of the

cases, coronary artery stenosis was observed, whilst in the remaining cases, complete segmental occlusion and corkscrew collaterals were noted. Approximately 38% of the patients underwent bypass surgery, 38% underwent medical treatment, including intravenous thrombolysis, and 24% underwent endovascular stenting or balloon angioplasty. The saphenous vein was most compatible for bypass surgery in comparison to the internal mammary artery due to the involvement of that artery. Of the patients who underwent bypass surgery, 80% recovered without bypass graft occlusion due to follow-up occurring approximately 1 year after surgery. About 67% of the vascular stents became occluded between surgery and the 5-month follow-up. All of the patients who received only conservative treatment, including vasodilators, showed improvement, and 67% of the patients who received thrombolytic treatments recovered. None of the patients died as a result of a cardiac event.

## Central nervous system

The systematic review revealed 15 articles related to the central nervous system. Four of the articles had been published in a language other than English and were excluded from our study. In total, 12 articles were included that comprised 12 patients and were published between 1952 and 2016 (Table 3). The mean age of the patients was  $35\pm 11$  years and 81% of the patients were male. The mean number of cigarettes smoked daily was  $30\pm 11$  and the duration of smoking before mesenteric ischemia was  $24\pm 18$  years. In 54% of the cases, TAO diagnosis had been made approximately 5 years before neurological complications. In the remaining cases, diagnosis occurred during or after neurological symptoms had developed. The clinical manifestations of the patients consisted of hemiparesis in 27% of the cases, aphasia in 18% of the cases, hemianopia in 13.5% of the cases, behavioral and cognitive impairment in 13.5% of the cases, seizure in 13.5% of the cases, hemiplegia in 10% of the cases, and severe localized headache in 4.5% of the cases. All five patients who completely stopped smoking improved. Vasodilators and anticoagulants did also result in improvement. However, 50% of the patients who received only anticoagulants and anti-platelets

showed improvement. The mortality rate due to cerebral ischemia was 8.3%.

## Eye

We located six articles related to the eye as a result of the systematic review. One article, published in 1988, reported on three cases of temporal arteritis for which TAO diagnosis was made after histology of the temporal artery. However, in the histology exam, the prominent infiltrating cells were eosinophils. Also, no additional data were available about the clinical manifestation of TAO in the extremities or any angiography examination. Therefore, due to its doubtful diagnosis of TAO, this study was excluded from our review. In total, we included five articles covering five patients that were published between 2006 and 2018 (Table 4). The mean age of the patients was  $57\pm 10$  years. All cases were male. The mean number of cigarettes smoked daily was  $15\pm 7$  and the duration of smoking before mesenteric ischemia was  $31\pm 11$  years. In all cases, eye involvement was observed after TAO diagnosis, which had occurred approximately 18 years earlier. The retinal artery was the most commonly involved artery. Receiving anti-platelets, either with or without corticosteroids, led to partial improvement. However, the treatment strategies and outcomes for 40% of the studies are unknown.

## Genitalia

According to a systemic search, we found six related articles. One article was not in English; therefore, it was excluded from our study. Totally, five articles were included which consisted of five patients in total and published between 1968 and 2016 (Table 5). The mean age of the patients was  $44\pm 20$  years and, in 60% of the cases, TAO diagnosis had occurred approximately 13 years before the urogenital events. No pharmaceutical treatment had been pursued for these patients.

## Kidneys

According to a systemic search, we found seven related articles. We could not have access to the full-text of two articles and one article was not in English. Therefore, they were excluded from our study. Totally, 4 articles included which consisted of 19 patients in total and published between 1959 and 2015 (Table 6). The mean

age of the patients was  $46\pm 8$  and all patients were male. In all cases, renal events had occurred approximately 8 years after TAO diagnosis. The pharmaceutical treatment for these patients is unknown. However, hepato-renal bypass grafting led to the improvement of renal function in one patient.

## Mucocutaneous zones

According to a systemic search, we found four related articles which consisted of five patients in total and published between 1980 and 2013 (Table 7). The mean age of the patients was  $39\pm 12$  years and, in 40% of the cases, skin events had occurred approximately 1.5 years before TAO diagnosis. In 60% of the cases, skin events had occurred approximately 5 years after TAO diagnosis. Stopping smoking and immunosuppressants, including methotrexate and corticosteroids but not vasodilators or anticoagulants, improved the skin lesions.

## Lymphohematopoietic system

According to a systemic search, we found six related articles. Three articles were not in English; therefore, they were excluded from our study. Totally, 3 articles were included which consisted of 28 patients in total and published between 1971 and 2016 (Table 8).

## Joints

The systematic review revealed four articles related to arthritis. We were not able to access the full text of one article and one article had been published in a language other than English. In total, we included 3 articles covering 13 patients that had been published between 1981 and 2003 (Table 9). The mean age of the patients was 45 years and, for one patient, TAO diagnosis was made after the experience of arthralgia. The medical treatment for the patients with arthralgia is unknown. However, one patient who received corticosteroids showed progression in the digital ischemia, despite joint improvement.

## Ear

According to a systemic search, we found one related article which consisted of one patient in total and published in 1962 (Table 10).

**Table 1** Data summary of patients with TAO and gastrointestinal tract involvement

No	Year	Authors	The number of patients	Age	Chief complaint	Duration of disease (amputation)	Smoking status	How to diagnose the current disease	Suggested treatment	The outcome of treatment
1	2016	Enshaei et al (Iran) <sup>3</sup>	1	39 years	Acute abdominal pain	Below-knee (BK) amputation 5 years earlier	1.5 packs of cigarette for 25 years	Previous diagnosis of TAO Abdominal X-ray laboratory tests Angiographic and histopathological examinations	Resection the gangrenous part of ileum (25 cm) following ileostomy	Two more laparotomy after the initial one because of the bilious discharge.
2	2016	Bouomrani et al (Tunisia) <sup>4</sup>	1	42 years	Recurrent duodenal ulcer lasting for 5 years which did not improve by the well- anti-ulcer treatment	Disease diagnosis 15 years earlier and two toe amputations during this time	Two packs of cigarettes for more than 15 years	Previous diagnosis of TAO according to clinical features, angiography and laboratory tests Endoscopy and histological examination of the ulcer	Anti-ulcer treatment in addition to anticoagulant and vasodilation treatment	Ulcer healing after two months confirmed by endoscopy No ulcer recurrence after four years follow-up
3	2016	Shastri et al (India) <sup>5</sup>	1	53 years	Diffuse abdominal pain with distention and constipation for 5 days following episodes of bloody stool, and bilious vomiting due to segmental ileum ischemia	Calf claudication 2 months earlier and gangrene of right 2nd and 5th toes 10 days earlier	One pack of cigarette for 20 years	TAO diagnosis according to clinical examination and laboratory tests Histological examination of ileum	Resection of 167 cm of ileum following anticoagulant treatment.	Recovery

(Continued)

Table 1 (Continued).

No	Year	Authors	The number of patients	Age	Chief complaint	Duration of disease (amputation)	Smoking status	How to diagnose the current disease	Suggested treatment	The outcome of treatment
4	2014	Kamiya et al (Japan) <sup>6</sup>	1	48 years (woman)	Acute severe and persisted abdominal pain	TAO diagnosis three years earlier She underwent below-knee amputation 3 years earlier and the diagnosis of TAO was confirmed by histological examination	Smoking one pack of cigarette daily before the disease diagnosis	Acute mesenteric artery occlusion in addition to multiple small infarctions in the kidneys was observed in the abdominal computed tomography Spleen infarction 1 day after the laparotomy The histological examination was not typical for TAO but more likely emboli. The source for emboli was thoracic aorta. However, the underlying cause of thrombus formation inside thoracic aorta remained elusive according to laboratory tests and intensive heart examination.	Resection of entire small intestine and the right side of the colon. Anti-coagulation therapy	Transient liver dysfunction after the surgery.

(Continued)

Table 1 (Continued).

No	Year	Authors	The number of patients	Age	Chief complaint	Duration of disease (amputation)	Smoking status	How to diagnose the current disease	Suggested treatment	The outcome of treatment
5	2010	Lee et al (Korea) <sup>7</sup>	2	Case 1: 65 years Case 2: 39 years	Case 1: Periumbilical and right lower quadrant pain with bloody diarrhea for 2 months. Pain worsening following constipation and abdominal distention in the last 3 days Case 2: Right lower quadrant pain and bloody stool for 5 days. Intermittent abdominal pain several months earlier.	Case 1: TAO diagnosis 16 years earlier and right BK amputation 11 years before colon ischemia Case 2: TAO diagnosis 5 years earlier according to clinical manifestation and angiography. He underwent toe amputation during this time	Case 1: smoking one pack of cigarette for 20 years but stopped smoking 3 years before colon ischemia. Case 2: one pack of cigarettes for 16 years	Case 1: Abdominal computed tomography Histological examination Case 2: Abdominal computed tomography Mesenteric angiography	Case 1: Rectosigmoid resection Case 2: Conservative treatment	Case 1- Recovery Case 2- Recovery
6	2009	Çakmak et al (Turkey) <sup>8</sup>	1	48 years	Postprandial abdominal pain and 25 kg weight loss within a year.	TAO diagnosis 14 years earlier and toe amputations during this time (Angiography confirmation)	Two packs of cigarette for 25 years	CT angiography of celiac trunk and superior and inferior mesenteric arteries Histopathological confirmation after hemicolectomy and ileum resection	First approach was angioplasty and stenting After 2 years, right hemicolectomy and partial ileum resection because of revascularization failure	Recovery
7	2009	Turkbey et al (Turkey) <sup>9</sup>	1	35 years	Increase in abdominal pain that was ongoing for 4 months	TAO diagnosis 20 years earlier and history of two BK amputation	Unknown	Abdominal CT angiography	Resection 200 cm of jejunum	Recovery

(Continued)

Table 1 (Continued).

No	Year	Authors	The number of patients	Age	Chief complaint	Duration of disease (amputation)	Smoking status	How to diagnose the current disease	Suggested treatment	The outcome of treatment
8	2006	Leung et al (NewYork, USA) <sup>10</sup>	1	34 years	Abdominal pain, nausea and vomiting with weight loss about 10 kg over 6 months.	TAO diagnosis according to clinical manifestation and angiography several weeks before mesenteric ischemia. The patient was under treatment with anticoagulants and calcium channel blocker	Lengthy history of smoking	According to Magnetic resonance imaging and abdominal CT scan. Small splenic and renal infarction was also observed. Histological examination of small intestine and superior mesenteric artery confirmed the diagnosis of TAO.	Resection of almost all of the small and large bowels	Discharged from hospital with hospice care at home.
9	2005	Cho et al (Korea) <sup>11</sup>	1	37 years	2-day history of diffuse abdominal pain and a 2-month history of claudication of his left hand	TAO diagnosis according to angiography and histological examination of small bowel	One pack of cigarette for 20 years	Abdominal CT scan. Histological examination of small intestine confirmed the diagnosis of TAO.	Resection of small bowel (40 cm)	Recovery
10	2003	Kobayashi et al (Japan) <sup>12</sup>	1	42 years	Abdominal pain with muscle guarding	TAO diagnosis according to Shionoya's criteria and excluding other types of vasculitis 8 months earlier and he had one BK amputation during this time. He was under treatment of warfarin and ticlopidine.	Two packs of cigarettes for 20 years	Angiography. According to autopsy and histological examination including posterior tibialis artery the diagnosis of TAO was confirmed.	The ileum end, cecum and proximal side of the ascending colon and sigmoid colon were necrotic and resected.	Death

(Continued)



Table 1 (Continued).

No	Year	Authors	The number of patients	Age	Chief complaint	Duration of disease (amputation)	Smoking status	How to diagnose the current disease	Suggested treatment	The outcome of treatment
11	2003	Cho et al (Korea) <sup>13</sup>	1	38 years	Obstipation and diffuse abdominal pain with 5 days duration	TAO diagnosis according to clinical manifestation and histological confirmation of minor amputation 14 years earlier The patient also underwent BK amputation during this time	One pack of cigarette for 18 days	Physical examination and emergency laparotomy Histology confirmed TAO diagnosis	Resection of 100 cm of small bowel	Unknown
12	2003	Kurata et al (Japan) <sup>14</sup>	1	35 years	Sudden onset of abdominal pain	TAO diagnosis 10 months earlier and lumbar sympathectomy during this time (Angiography characteristics for TAO)	One pack of cigarette for 15 years	Abdominal X-Ray and emergency laparotomy Histology confirmed TAO diagnosis	Resection of small bowel including ileocecal (54 cm)	Recovery
13	2001	Sidiqui et al (NewYork, USA) <sup>15</sup>	1	51 years	7-month history of abdominal pain and under corticosteroid treatment by the diagnosis of Crohn's disease Acute abdominal pain in the hospital due to non-healing ulcer of ingrown toenail	TAO diagnosis at the onset of acute abdomen by lower limb angiography The diagnosis was confirmed by histological exam after autopsy	Smoking for 26 years	Abdominal CT scan -Aortogram -Angiography Histology confirmed TAO diagnosis	Plasmapheresis and high-dose steroids temporary improvement but small bowel resection (36 cm) 2 months later	Death due to recurrent intestinal ischemic perforations, and sepsis
14	2001	Hassoun et al (Belgium) <sup>16</sup>	1	50 years	3-month history of postprandial epigastric pain, vomiting, and diarrhea and weight loss around 15 kg over the past 5 months	TAO diagnosis 30 years earlier and one BK and several minor amputations during this time	One pack of cigarette for 32 years	Abdominal CT scan Angiography	Conservative treatment	Recovery

(Continued)

Table 1 (Continued).

No	Year	Authors	The number of patients	Age	Chief complaint	Duration of disease (amputation)	Smoking status	How to diagnose the current disease	Suggested treatment	The outcome of treatment
15	1998	Iwai (Japan) <sup>17</sup>	3	Case 1: 51 years Case 2: 43 years Case 3: 43 years (identical twin of case 2)	Case 1: Epigastric pain Case 2: Postprandial abdominal pain for 2 years following 15 kg weight loss in one year Case 3: abdominal angina	Case 1: TAO diagnosis according to clinical manifestation and angiography 10 years earlier Case 2: TAO diagnosis according to the time of abdominal pain according to clinical manifestation and lower limb angiography Case 3: TAO diagnosis at the time of abdominal angina according to clinical manifestation of lower limbs and angiography and aortography	Case 1: one pack of cigarettes for 30 years Case 2: unknown Case 3: unknown	Case 1: Upper GI series showed deformity of the duodenal bulb and ulcer formation. Histology of right gastric artery was compatible with diagnosis of TAO Case 2: Aortography Case 3: Aortography Histology of splenic artery was compatible with TAO diagnosis	Case 1: Gastrectomy Case 2: bypass revascularization and sympathectomy of mesentric and celiac ganglia Case 3: Bypass surgery	Case 1- Recovery Case 2- Failure of vascular reconstruction two years after bypass surgery Case 3- Recovery
16	1998	Michail et al (Greece) <sup>18</sup>	1	42 years	History of chronic abdominal pain Reported with acute abdominal pain and vomiting	TAO diagnosis according to clinical manifestation and angiography at the time of hospital admission	Heavy smoker for 24 years	Abdominal X-rays Angiography Histology confirmed TAO diagnosis	Partial enterectomy	Recovery
17	1998	Lie (California, USA) <sup>19</sup>	4	Range from 35 to 41 years	Unknown	Duration of the disease is unknown but all the cases had at least one leg amputations	Unknown	Unknown But ileum, ascending colon, jejunum and sigmoid colon were infarcted or gangrenous in the four cases	Resection of ileum and ascending colon in two cases Other two cases died before surgical intervention	50% Death

(Continued)

Table 1 (Continued).

No	Year	Authors	The number of patients	Age	Chief complaint	Duration of disease (amputation)	Smoking status	How to diagnose the current disease	Suggested treatment	The outcome of treatment
18	1996	Sauvaget et al (France) <sup>20</sup>	1	36 years	Dysentery associated with a weight loss of 12 kg following acute abdomen	TAO diagnosis at the workup for the cause of dysentery Angiography of the lower limbs were characteristics for TAO	17 pack-year	Colonoscopy which showed diffuse superficial ulcerations, with a deep ulceration of the sigmoid colon. Unresponsive to amebicides Histology exam confirmed TAO diagnosis	Resection of sigmoid 17 cm Intravenous heparin and prostacyclin	Recovery
19	1995	Burke et al (Washington, USA) <sup>21</sup>	2	Case 1: 39 years Case 2: 48 years	Unknown	Unknown	Heavy smokers	Unknown Histology exam confirmed TAO diagnosis	Unknown	Case 1- Recovery Case 2- recurrent strictures at bowel anastomosis during 4 years follow-up
20	1994	Schellong et al (Germany) <sup>22</sup>	1	23 years	9-month history of postprandial abdominal pain and weight loss about 15 kg Referred from another hospital by diagnosis of mesenteric ischemia confirmed by angiography	TAO diagnosis at the workup for the acute abdominal pain	20-30 cigarettes for 5 years	Abdominal examination Angiography Raising liver enzymes -Histologic examination was compatible with TAO	Thrombectomy and short vein bypass from the aorta to the common hepatic artery	Recovery
21	1994	Saboya et al (Brasil) <sup>23</sup>	1	34 years	Because of 8 hrs intestine pain in the lower abdomen and obstipation	Two BK amputations 2 years earlier	Unknown but give up smoking for 2 years	Laparotomy due to abdominal examination and laboratory tests Histology was supportive for TAO	Resection of sigmoid colon (28 cm was necrotic) and rectum	Discharged with colostomy

(Continued)

Table 1 (Continued).

No	Year	Authors	The number of patients	Age	Chief complaint	Duration of disease (amputation)	Smoking status	How to diagnose the current disease	Suggested treatment	The outcome of treatment
22	1993	Ito et al (Japan) <sup>24</sup>	1	42 years	Acute right lower quadrant pain and with severe tenderness and slight muscle guarding previous history of abdominal colicky pain and vomiting	TAO diagnosis 14 years earlier and two BK amputations during this time and several toe amputations	30 cigarettes daily for 20 years	Laparotomy by primary diagnosis of diverticulitis (The patient had appendectomy before) Postoperative aortography and histology of cecum and small mesenteric vessels confirmed TAO diagnosis	Ileocecal resection	Recovery
23	1993	Broide et al (Israel) <sup>25</sup>	1	20 years	Severe abdominal pain and vomiting of 3 days duration	TAO diagnosis 2 years after acute abdomen according to clinical manifestations, laboratory investigation and angiography	Two to three packs of cigarette for 5 years	Retrograde diagnosis of TAO for mesenteric ischemia	Resection of jejunum Histology demonstrated well-organized thrombi in branches of superior mesenteric artery	Recovery
24	1983	Soo et al (Australia) <sup>26</sup>	1	48 years	Abdominal pain in right iliac fossa with rebound and tenderness	TAO diagnosis 7 years earlier according to clinical manifestation The patient underwent one BK amputation and several toe amputations Histology examination confirmed the diagnosis of TAO	Three packs of cigarette a day	The pre-operative diagnosis was appendicitis During the surgery 8 cm infarcted sigmoid colon was observed. Histology study confirmed the diagnosis of TAO in the colon. Appendix was macroscopic and microscopic normal.	Resection of sigmoid colon	Recovery

(Continued)

Table 1 (Continued).

No	Year	Authors	The number of patients	Age	Chief complaint	Duration of disease (amputation)	Smoking status	How to diagnose the current disease	Suggested treatment	The outcome of treatment
25	1979	Borlaza et al (Michigan, USA) <sup>27</sup>	1	36 years	2-week history of abdominal pain with nausea and vomiting and weight loss	TAO diagnosis after abdominal pain according to clinical manifestation, angiography of lower limbs	Two packs of cigarettes per day for 21 years	Laparotomy by initial diagnosis of intussusception and resection of ileum. Histology findings were suggestive for BD. Aortography was also supportive for visceral TAO.	Resection of ileum (30 cm)	Recovery
26	1979	Sobel et al (California, USA) <sup>28</sup>	1	35 years	During hospital admission for non-healing wound of amputation stump, the patient developed abdominal pain following decreased consciousness and generalized seizure	TAO diagnosis 10 years earlier and one BK amputation. Histology had confirmed TAO.	One to two packs of cigarette for 25 years	In autopsy, necrotic pancreas and infarcted spleen due to occlusion of celiac and splenic artery and hemorrhagic bilateral adrenal necrosis and hemorrhagic infarction of pituitary and cerebral cortices. Histology of celiac artery was supportive for TAO diagnosis.	Nothing for the abdominal pain due to acute renal failure	Death
27	1977	Sachs et al (Texas, USA) <sup>29</sup>	1	45 years	Constant left upper quadrant abdominal pain. History of 1 year anorexia and weight loss.	TAO diagnosis at the time of admission for abdominal pain.	Two packs of cigarettes for 30 years	Barium enema and aortography. Histology was supportive for TAO diagnosis.	Resection of transverse colon	Unknown

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Table 1 (Continued).

No	Year	Authors	The number of patients	Age	Chief complaint	Duration of disease (amputation)	Smoking status	How to diagnose the current disease	Suggested treatment	The outcome of treatment
28	1972	Wolf et al (Washington, USA) <sup>30</sup>	2	Case 1: 53 Case 2: 43	Case 1: Obstipation and persistent abdominal pain with vomiting Case 2: Reporting with gastrointestinal hemorrhage and shock Nausea and cramping abdominal pain 5 days before admission.	Case 1: BD diagnosis 18 years earlier and one BK amputation during this time Case 2: BD diagnosis 2 years earlier and one BK amputation Histology confirmed the diagnosis of TAO	Case 1: 30 cigarettes per day for 38 years Case 2: 20 to 40 cigarettes per day for 30 years	Case 1: Abdominal examination and exploring laparotomy which showed two small abdominal wall abscesses Since the abscesses could not explain the pain of the patient, biopsy from jejunal mesenteric arcade was obtained The histological findings were supportive for visceral BD Case 2: At autopsy, thrombosis of portal vein, which extended into the superior mesenteric vein and the infarction of jejunum histology demonstrated neutrophilic infiltration of vein wall	Case 1: Unknown Case 2: Death	

(Continued)

Table 1 (Continued).

No	Year	Authors	The number of patients	Age	Chief complaint	Duration of disease (amputation)	Smoking status	How to diagnose the current disease	Suggested treatment	The outcome of treatment
29	1968	Herrington et al (Tennessee, USA) <sup>31</sup>	2	Case 1: 33 years Case 2: 42 years	Case 1: Several days of cramping, left lower quadrant abdominal pain following severe tenderness Case 2: 8 months cramping abdominal pain, anorexia, and weight loss of 20 pounds following severe abdominal pain	Case 1: TAO diagnosis at the onset of acute abdomen according to past medical history and clinical manifestation and histology exam of the sigmoid colon Case 2: TAO diagnosis at the onset of acute abdomen. Angiography of upper and lower limbs confirmed the diagnosis of TAO	Case 1: Smoking for years Case 2: Smoking 60 cigarettes per day for 24 years	Case 1: Laparotomy by the suspicious of sigmoid diverticulitis Histology confirmed TAO diagnosis Case 2: laparotomy by the primary diagnosis of appendicitis. However, appendices was normal but jejunum was ischemic.	Case 1: Resection of sigmoid colon Case 2: Resection of jejunum (60 cm)	Case 1: Recovery Case 2: Recovery after resection of jejunum but 1 month later he had massive melena and then death
30	1966	Rob et al (New York, USA) <sup>32</sup>	1	46 years	Cramping and spasmodic, central abdominal pain associated with diarrhea and weight loss	TAO diagnosis many years earlier and two BK amputations during this time	Unknown	Abdominal X-ray Aortography was normal however the histological exam of the resected bowel confirmed the diagnosis of TAO in the thrombotic occluded vessels in the mesentery	Resection the ischemic part of small bowel	Unknown

(Continued)

Table 1 (Continued).

No	Year	Authors	The number of patients	Age	Chief complaint	Duration of disease (amputation)	Smoking status	How to diagnose the current disease	Suggested treatment	The outcome of treatment
31	1953	Kilbourne et al (Chicago, USA) <sup>33</sup>	1	35 years	Epigastric pain, vomiting and blood loss in stool	TAO diagnosis 1 year earlier and one BK amputation	Heavy smokers	Laparotomy by primary diagnosis of superimposed polyps or Carcinoma. During the surgery stomach was found to be 3 to 4 times normal thickness and somewhat spongy from cardia to antrum, where there was an abrupt change to normal consistency and thickness. perigastric nodes were enlarged up to 4 by 2 cm. Histology demonstrated no malignancy but perivascular inflammation without thrombotic occlusion.	The involved portion of the stomach was resected	Recovery
32	1947	Garvin (Pennsylvania, USA) <sup>34</sup>	1	33 years	Abdominal pain, distention and vomiting. History of same presentation 8 years earlier	TAO diagnosis 8 months earlier	Unknown	Laparotomy by diagnosis of mesenteric ischemia. The histology was supportive for TAO diagnosis	Resection 45 cm of gangrenous proximal ileum	Unknown



**Table 2** Data summary of patients with TAO and coronary arteries involvement

No	Year	Authors	The number of patients	Age	Chief complaint	Duration of disease (amputation)	Smoking status	How to diagnose the current disease	Suggested treatment	The outcome of treatment
1	2018	Tekin et al (Turkey) <sup>35</sup>	1	45 years	Acute chest pain	TAO diagnosis 2 years earlier	25 pack/year	Angiography coronary dissection in LAD	Bypass surgery using saphenous vein	Recovery no data about further follow-up
2	2016	Atay et al (Turkey) <sup>36</sup>	1	26 years	Chest pain and myocardial infarction two times in 1 year	TAO diagnosis before the chest pain confirmed by angiography	Unknown	Coronary angiography 70% stenosis of LAD	Angioplasty with drug-induced stent Balloon angioplasty for in-stent thrombosis and thrombolytic therapy Cilostazol	Stent thrombosis 5 months later No more data about the condition of the patient after balloon angioplasty and receiving Cilostazol
3	2013	Mitropoulos et al (Greece) <sup>37</sup>	1	52 years	Myocardial infarction	TAO diagnosis 25 years earlier One BK and several minor amputations	Heavy smoker	CT angiography 80–90% stenosis of LAD	Bypass surgery	Recovery and improved ejection fraction after one year follow-up

(Continued)

Table 2 (Continued).

No	Year	Authors	The number of patients	Age	Chief complaint	Duration of disease (amputation)	Smoking status	How to diagnose the current disease	Suggested treatment	The outcome of treatment
4	2013	Akyuz et al (Turkey) <sup>38</sup>	1	43 years	Onset of severe chest pain and loss of consciousness due to inferior and right myocardial infarction	TAO diagnosis 5 years earlier	Unknown	Coronary angiography showed total occlusion of mid-portion LAD and proximal RCA without any flow	Unsuccessful endovascular procedure and because of unstable hemodynamic could not be candidate for bypass surgery Tissue plasminogen activator (tPA) and glycoprotein IIb/IIIa inhibitor	Recovery No data about further follow-up
5	2007	Hsu et al (Taiwan) <sup>39</sup>	1	32 years	Acute chest tingling for 2 hrs with V1-V6 ST elevation which recovered spontaneously. Also frequent episodes of accelerated idioventricular rhythm	Previous TAO diagnosis with angiography confirmation	Unknown	Coronary angiography 90% stenosis of proximal LAD	Stent implantation	Recovery No data about further follow-up
6	2007	Abe et al (Japan) <sup>40</sup>	1	38 years	Unknown but coronary angiography was performed during the hospital admission of the patient for ischemic leg pain at rest	TAO diagnosis 13 years earlier	Unknown	Coronary angiography complete occlusion of the middle segment of LAD and corkscrew collaterals and intact right coronary artery supplied blood stream distally	Unknown	Unknown

(Continued)

Table 2 (Continued).

No	Year	Authors	The number of patients	Age	Chief complaint	Duration of disease (amputation)	Smoking status	How to diagnose the current disease	Suggested treatment	The outcome of treatment
7	2006	Miranda (Lebanon) <sup>41</sup>	1	60 years	Non-ST-elevation myocardial infarction and dyspnea after left upper lobe lung resection for non-small-cell lung cancer.	A known case of TAO	Unknown	Coronary angiography showed a 90% stenosis of the distal RCA with distal flow via collaterals Chest CT scan showed thrombosis in the left upper pulmonary vein	RCA stenting Oral anticoagulation	Recovery and complication after 3 months follow-up
8	2005	Hong et al (Chicago, USA) <sup>42</sup>	1	61 years	Referred for a positive stress test	TAO diagnosis 32 years earlier One BK, one above elbow and several minor amputations	50 pack/year	Coronary angiography No significant narrowing of LAD, the first diagonal artery, there were multiple, sequential, intraluminal filling defects in a beaded pattern. The left circumflex artery had a 40% stenosis in its proximal portion with 2 filling defects at the onset of the first obtuse marginal artery. The right coronary artery had a focal 60% stenosis in its mid portion with an overlying filling defect resulting in a 90% stenosis	Aspirin and Warfarin	No change in the angiography after 2 months follow-up
9	2002	Becit et al (Turkey) <sup>43</sup>	1	36 years	Acute chest pain, palpitation and sweating due to acute anteroapical myocardial infarction	TAO diagnosis 12 years earlier	One pack of cigarette per day for 8 years previous to TAO diagnosis	Coronary angiography revealed total occlusion of the proximal segment of LAD and plaque at RCA. Histology examination of an endarterectomy specimen showed specific feature of TAO	Closed endarterectomy and bypass surgery using saphenous vein and left internal mammary artery	Symptoms free up to 7 months after bypass surgery because of the occlusion of distal bypass graft.

(Continued)

Table 2 (Continued).

No	Year	Authors	The number of patients	Age	Chief complaint	Duration of disease (amputation)	Smoking status	How to diagnose the current disease	Suggested treatment	The outcome of treatment
10	2002	Hoppe et al (California, USA) <sup>44</sup>	1	39 years (woman)	Three-hour of retrosternal chest pain. History of similar episode of chest pain, which resolved spontaneously, 2 weeks earlier	History of TAO diagnosis	Unknown (Smoker)	Coronary angiography a proximally occluded LAD that filled distally via right to left collaterals, a 50% proximal left circumflex coronary and a dominant right coronary artery that had proximal to mid-vessel beaded irregularities The histology examination of the left internal mammary artery confirmed TAO diagnosis	Bypass surgery	Recovery No data about follow-up
11	1997	Francesco Donatelli et al (Italy) <sup>45</sup>	1	39 years (woman)	Unstable angina History of 2 years epigastric pain of unknown origin and sporadic episodes of typical angina for the past 8 months	TAO diagnosis according to histology examination of internal thoracic artery and excluding other types of vasculitis No more information about the extremities	She had never smoked	Coronary angiography, stenosis of LAD artery and RCA. Histology examination of dissected internal thoracic arteries was compatible with TAO diagnosis.	Bypass surgery of three vessels with saphenous veins Internal thoracic arteries were not suitable for grafting because of diffuse narrowing at the proximal end and occlusion at the distal end. Note: satellite lymph nodes were enlarged.	Recovery and no onset of any angina during 8 months follow-up

(Continued)

Table 2 (Continued).

No	Year	Authors	The number of patients	Age	Chief complaint	Duration of disease (amputation)	Smoking status	How to diagnose the current disease	Suggested treatment	The outcome of treatment
12	1993	Mautner et al (New York, USA) <sup>46</sup>	1	37 years	Prolonged chest pain with T-wave inversion in leads I, aVL, and V4 to V6	TAO diagnosis is unknown because the histology report of coronary arteries during autopsy is more supportive for diffuse atherosclerosis	One pack of cigarettes for 15 years	Coronary angiography About 75% stenosis of left circumflex coronary artery	Intravenous streptokinase	Death due to mesenteric ischemia
13	1987	Kim et al (Korea) <sup>47</sup>	1	29 years	Continuous substernal chest pain for 3 days due to anterior myocardial infarction	TAO diagnosis at the time of admission for chest pain confirmed by upper and lower limbs angiography	Unknown	Coronary angiography Segmental occlusion of proximal LAD Complete occlusion of the first diagonal branch of LAD in the distal portion, irregular and tortuous contour of RCA without obvious luminal narrowing	Conservative treatment with nitrate, beta blocker and calcium channel blocker	Recovery No data about the duration of follow-up
14	1985	Ohno et al (Japan) <sup>48</sup>	1	32 years	Severe chest pain at rest for 3 hrs due to acute myocardial infarction	TAO diagnosis 6 years earlier and one BK and one toe amputation during this time	41–60 cigarettes per day for 12 years	Coronary angiography revealed 70% stenosis of RCA and the proximal LAD	Urokinase Discharged with vasodilator and anticoagulant therapy	Recovery (About 1 month follow-up)

**Table 3** Data summary of patients with TAO and cerebral arteries involvement

No	Year	Authors	The number of patients	Age	Chief complaint	Duration of disease (amputation)	Smoking status	How to diagnose the current disease	Suggested treatment	The outcome of treatment
1	2016	Aydin et al (Turkey) <sup>49</sup>	1	30 years	Acute onset left hemiparesis	TAO diagnosis 8 years earlier Angiography of upper and lower limbs were compatible with TAO diagnosis	Unknown	MRI demonstrated showed infarct of right basal ganglia MRA and MIP of cerebral artery demonstrated segmental occlusions bypassed by collaterals	Unknown	Unknown
2	2013	Akyuz et al (Turkey) <sup>38</sup>	1	43 years	Blurred consciousness and right hemiplegia and right hemianopsia during hospitalization for myocardial infarction	TAO diagnosis 5 years earlier	Unknown	Cranial CT scan demonstrated left posterior cerebral artery territory infarct	Tissue plasminogen activator (tPA) and glycoprotein IIb/IIIa inhibitor	Fully recovered from hemiplegia and partially recovered from hemianopsia
3	2012	Hurelbrink et al (Australia) <sup>51</sup>	1	56 years (woman)	Cognitive decline over 18 months started with global aphasia and gradually became dependent for the basic self-care activities. After then her memory and mood were also affected	TAO diagnosis according to the pathology report of white leptomeningeal vessels and excluding other types of vasculitis or hyper-coagulable state responsible for neurological manifestation	25–30 cigarettes per day for more than 30 years	MRI and cerebral angiography demonstrated terminal vessel occlusions associated with widespread proliferation of new vessels	Smoking cessation	Improvement
4	2007	Huang et al (Taiwan) <sup>50</sup>	1	57 years	Sudden onset right limb numbness and crossed sensory deficit over the left side of his face and right side of his trunk and extremities, a left homonymous hemianopsia and limitation in eye movements.	TAO diagnosis during hospitalization for neurological complaints by excluding other types of vasculitis or hyper-coagulable state and angiography of upper limb	One pack of cigarettes for 42 years	According to neurological exam, diagnosis of left pontine infarct and right occipital infarct was made	Smoking cessation and vasodilators and anti-platelets	Improvement in acrocyanosis but unknown about neurological manifestation

(Continued)

Table 3 (Continued).

No	Year	Authors	The number of patients	Age	Chief complaint	Duration of disease (amputation)	Smoking status	How to diagnose the current disease	Suggested treatment	The outcome of treatment
5	2005	No et al (Korea) <sup>51</sup>	1	29 years	Sudden onset of 20-min episodes of a tingling sensation in his left face, arm and leg during a week. History of hemiparesis 6 years earlier which improved within a week	TAO diagnosis at the time of admission according to clinical manifestation, CT angiography and excluding other types of vasculitis vasculitis or hyper-coagulable state	More than 40 cigarettes a day for 11 years	Brain MRI angiography demonstrated multiple tandem arterial occlusions in the middle cerebral arteries with fine collaterals around the occluded segments	Intravenous prostaglandin E1 following aspirin and Clopidogrel And smoking cessation	Recovery and no recurrence of the symptoms in 1 year follow-up
6	1998	Bischof et al (Germany) <sup>52</sup>	1	26 years	10-day history of severe left-sided headache and episodes of transient sensorimotor right sided hemiparesis and aphasia which lasted for 20 mins and resolved completely	TAO diagnosis 2 years earlier according to clinical manifestation, capillaroscopy and ultrasound examination Other types of vasculitis vasculitis or hyper-coagulable state were also excluded.	20 cigarettes a day	Brain MRI demonstrated thrombosis of superior sagittal sinus	Intravenous heparin which changed into oral anticoagulation	Recovery and no relapse within 2 weeks follow-up

(Continued)

Table 3 (Continued).

No	Year	Authors	The number of patients	Age	Chief complaint	Duration of disease (amputation)	Smoking status	How to diagnose the current disease	Suggested treatment	The outcome of treatment
7	1995	Dotti et al (Italy) <sup>53</sup>	1	30 years	Behavioral disturbances with severe cognitive impairment. History of grand-mal-type epileptic seizure at age 17	TAO diagnosis 6 years earlier according to clinical manifestation and angiography and one BK amputation and two finger amputations	Heavy smoker for many years	Digital angiography of the aortic arch and cerebral arteries showed occlusion of the left subclavian meningism and the presence of a corresponding collateral circulation Brain MRI showed mild atrophy of the corpus callosum, diffuse white matter signal alterations suggesting a process of gliosis and a small ischemic lesion of the thalamus	Unknown	Unknown

(Continued)



Table 3 (Continued).

No	Year	Authors	The number of patients	Age	Chief complaint	Duration of disease (amputation)	Smoking status	How to diagnose the current disease	Suggested treatment	The outcome of treatment
8	1984	Kessler et al (Germany) <sup>54</sup>	1	26 years	Right optic neuritis History of major epileptic seizure with left spastic hemiparesis, left hyperesthesia, left hyperreflexia with a left positive Babinski response 2 months earlier History of left hemiparesis 9 months earlier History of reeling gait and dizziness 1 year earlier History of blurred vision of left eye for a few days 2 years earlier	Unknown	40 cigarettes per day from his early youth	Brain CT scan showed small areas of hypodensity CSF examination	Corticosteroid therapy	Improvement
9	1982	Drake(Ohio, USA) <sup>55</sup>	1	27 years	Onset of right hemiparesis and sensory loss	TAO diagnosis 5 years later according to clinical manifestation, angiography characteristics and normal laboratory tests	50 cigarettes per day for 12 years	Brain CT scan, CSF examination Angiography showed occlusion of posterior cerebral artery	Aspirin Dipyridamole	Some resolution of neurological deficit but relapses as dysarthria and new left-sided weakness 8 months later

(Continued)

Table 3 (Continued).

No	Year	Authors	The number of patients	Age	Chief complaint	Duration of disease (amputation)	Smoking status	How to diagnose the current disease	Suggested treatment	The outcome of treatment
10	1981	Biller et al (North Carolina, USA) <sup>56</sup>	1	33 years (Woman)	Sudden inability to talk and swallow History of left hemiparesis 7 years earlier	TAO diagnosis 6 years earlier confirmed by upper and lower limbs angiography and histology examination of toes and fingers amputations	10 cigarettes a day for many years	Radionuclide brain scan and CT scan showed an area of infarction in the left fronto-opercular area aortocranial arteriography showed exaggerated tapering of the proximal segments of both middle cerebral artery branches, predominantly at the level of the frontal opercula	Unknown	Partial improvement
11	1958	Wolman (UK) <sup>57</sup>	1	26 years	Pseudobulbar palsy after a severe seizure with gross emotional lability History of series of left-sided seizures despite being on anticonvulsant treatment from 1 year earlier.	TAO diagnosis by histology study after autopsy	Unknown	Histology examination of cerebral arteries following autopsy demonstrated TAO characteristics in the right and left middle cerebral arteries and their branches	Anticonvulsant drugs	Death
12	1952	Lippmann (New York, USA) <sup>58</sup>	1	34 years	Right spastic hemiplegia, motor aphasia, right hemianesthesia, right central facial palsy and right hyper-reflexia History of right hemiplegia and aphasia for 2 days History of a few days speech deterioration	TAO diagnosis 2 years earlier and one BK amputation	Heavy smoker since early adulthood	According to clinical examination, diagnosis of left middle cerebral artery occlusion	Smoking cessation	No progression in the disease, not in the limbs nor any neurological onset was observed during 31 years follow-up and the patient completely stopped smoking

Table 4 Data summary of patients with TAO and eye involvement

No	Year	Authors	The number of patients	Age	Chief complaint	Duration of disease (amputation)	Smoking status	How to diagnose the current disease	Suggested treatment	The outcome of treatment
1	2018	Korkmaz et al (Turkey) <sup>59</sup>	1	43 years	Onset of low vision in the left eye due to nonarteritic anterior ischemic optic neuropathy	TAO diagnosis 7 years earlier according to clinical Shionoya's criteria, CT angiography and excluding other types of vasculitis or hyper-coagulable state. He was under treatment of Cilostazol	One pack of cigarette a day for 20 years	Eye examination including fluorescein angiography brain/orbits MRI and MR venography with and without contrast	Aspirin (300 mg/daily) and oral steroid (prednisone, 1 mg/kg/daily, 14 days)	Partial improvement at the 4th day of treatment
2	2017	Eris et al (Turkey) <sup>60</sup>	1	64 years	Onset of acute painless vision loss in his left eye due to central retinal artery occlusion	TAO diagnosis from 32 years earlier and one BK amputation during this time	Smoking for 43 years	Eye examination including fluorescein angiography	Hyperbaric oxygen therapy for 20 sessions	Partially improvement
3	2015	Marques et al (Portugal) <sup>61</sup>	1	64 years	Progressive bilateral visual acuity decrease and nyctalopia due to extensive chorioretinal atrophy	TAO diagnosis about 30 years earlier and several minor amputations during this time	Previous smoker (15 pack/year)	Eye examination including fluorescein angiography	Aspirin (150 mg/daily)	Partially improvement during 1 year follow-up
4	2014	Koban et al (Turkey) <sup>62</sup>	1	48 years	Acute vision loss in the left eye due to acute inferonasal branch retinal artery occlusion and bilateral normal tension glaucoma	TAO diagnosis 12 years earlier and two BK amputations during this time	Unknown	Eye examination including fluorescein angiography Cranial MRI	Unknown	Unknown
5	2006	Ohguro et al (Japan) <sup>63</sup>	1	66 years	Progressive visual field disturbance in the left eye due to normal tension glaucoma with branch retinal artery occlusion	TAO diagnosis 10 years earlier and history of myocardial infarction during this time	Unknown	Eye examination including fluorescein angiography Cranial MRI	Unknown	Unknown

Table 5 Data summary of patients with TAO and genitalia involvement

No	Year	Authors	The number of patients	Age	Chief complaint	Duration of disease (amputation)	Smoking status	How to diagnose the current disease	Suggested treatment	The outcome of treatment
1	2016	Pham et al (Massachusetts, USA) <sup>64</sup>	1	56 years	Gangrenous glans penis history of recurrent penile and scrotal ulcers during 1 year	TAO diagnosis 4 years earlier	80 pack-year from his earlier teens	Physical examination	Partial penectomy with urethral reconstruction Histology confirmed TAO diagnosis	Unknown
2	2016	Roberts et al (Australia) <sup>65</sup>	1	17 years	3 weeks history of testicular mass and a painless swelling in the left hemiscrotum	TAO diagnosis according to testicular histology examination	Tobacco and cannabis smoker	Physical exam, ultrasonography and laboratory tests Histology showed multiple infarcts of the testicular parenchyma with an obliterated artery adjacent to each infarct. The histology of occlusions was compatible with TAO diagnosis	Left inguinal orchiectomy by	No further follow-up
3	2008	Aktoz et al (Turkey) <sup>66</sup>	1	47 years	Scrotal and penile necrosis	TAO diagnosis 1 year earlier according to clinical manifestation and MRA imaging of the lower limbs and one AK amputation	Two packs of cigarettes for 30 years	Physical exam Histology examination of scrotal tissues was compatible with TAO diagnosis	Partial penectomy, scrotal debridement and urethra-cutaneous anastomosis	Unknown
4	2004	Orhan et al (Turkey) <sup>67</sup>	1	70 years	Painful gangrene half of the penile shaft and the glans	TAO diagnosis 34 years earlier and two AK and several minor amputations during this time	Smoking for 55 years	Physical examination Pathology examination confirmed TAO diagnosis	Partial penectomy	Unknown

(Continued)

**Table 5** (Continued).

No	Year	Authors	The number of patients	Age	Chief complaint	Duration of disease (amputation)	Smoking status	How to diagnose the current disease	Suggested treatment	The outcome of treatment
5	1968	Herrington et al (Tennessee, USA) <sup>31</sup>	1	33 years	Suddenly thrombosis of the dorsal vein of the penis and gangrene of the distal two thirds of that organ with perforation of the urethra during hospitalization for mesenteric ischemia	TAO diagnosis at the onset of acute abdomen according to past medical history and clinical manifestation and histology exam of the sigmoid colon before penile gangrene	Smoking for years	Physical examination	Extensive plastic and urologic procedures.	No more relapses during 5 years follow-up

**Table 6** Data summary of patients with TAO and renal involvement

No	Year	Authors	The number of patients	Age	Chief complaint	Duration of disease (Amputation)	Smoking status	How to diagnose the current disease	Suggested treatment	The outcome of treatment
1	2015	Yun et al (Korea) <sup>68</sup>	1	51 years	Severe left flank pain, hematuria, and oliguria for 3 days And history of 1 year hypertension	TAO diagnosis 10 years earlier confirmed by extremity angiography and Two big toes amputations under treatment with beraprost	One pack of cigarettes for 30 years	Abdominal CT scan Aortography which demonstrated occlusion of superior and inferior mesenteric artery, both renal arteries and left common iliac artery with well-developed collaterals	Peritoneal dialysis with warfarin	Postprandial pain and ischemic transverse colon Dialysis changed into hemodialysis
2	2006	Goktas et al (Turkey) <sup>69</sup>	1	37 years	Fever, right flank pain and weakness due to right kidney infarction	TAO diagnosis 7 years earlier	Heavy smoker	Abdominal CT scan Angiography showed stenosis in the intra-renal branches of right renal artery	Unknown	Unknown

(Continued)

Table 6 (Continued).

No	Year	Authors	The number of patients	Age	Chief complaint	Duration of disease (Amputation)	Smoking status	How to diagnose the current disease	Suggested treatment	The outcome of treatment
3	2003	Stillaert et al (Belgium) <sup>70</sup>	1	51 years	Uncontrollable hypertension and episodes of oligo-anuria which developed during 2 weeks	Previous TAO diagnosis and two AK-amputations 8 years earlier	20 cigarettes per day	MRA showed a severe stenosis of the right renal artery and an occluded left renal artery.	Right hepato-renal bypass grafting	Normal right renal function was maintained at 1-year follow-up.
4	1959	Fida et al (Italy) <sup>71</sup>	16 (16 out of 52 TAO cases)	Ranged from 23 to 49 years	Disturbed renal function	TAO diagnosis confirmed by angiography	Unknown	Urine analysis GFR, RPF, RBF, Maximal rate of tubular excretion Renal biopsies	Unknown	Unknown

Table 7 Data summary of patients with TAO and involvement of mucocutaneous zones

No	Year	Authors	The number of patients	Age	Chief complaint	Duration of disease (Amputation)	Smoking status	How to diagnose the current disease	Suggested treatment	The outcome of treatment
1	2013	Li et al (China) <sup>72</sup>	2 brothers	Case 1: 33 years Case 2: 27 years	1: Erythema nodosum in the bilateral lower leg extensors and the dorsum of the right foot, without evident causes 2: Erythema nodosum on the left shank and the top of the left foot accompanied by numbness and pain in the feet, without evident reason	Case 1: 8 years earlier Case 2: 3 years earlier	Case 1: 5-8 cigarettes per day for 10 years Case 2: 3-5 cigarettes per day for 4 years	Case 1: Skin biopsy confirmed erythema nodosum diagnosis Case 2: Physical exam	Case 1: Immune suppression treatment with methotrexate, triptriolide, cyclophosphamide, prednisolone and methylprednisolone Case 2: Hormonal and microcirculation therapy (no more details)	Case 1: Improvement with leaving a small level of pigmentation on the skin Case 2: Improvement

(Continued)

Table 7 (Continued).

No	Year	Authors	The number of patients	Age	Chief complaint	Duration of disease (Amputation)	Smoking status	How to diagnose the current disease	Suggested treatment	The outcome of treatment
2	2007	Takanashi et al (Japan) <sup>73</sup>	1	33 years	Painful nodular erythema with livedo reticularis in both lower extremities	TAO diagnosis 2 years later according to clinical manifestation, angiography characteristics and histology examination of toe amputation	30 cigarettes per day for 15 years	Skin biopsy	Oral prednisolone (20 mg daily) and NSAIDs	Recovery of skin symptoms
3	1981	Queneville et al (Canada) <sup>74</sup>	1	44 years	Painful subcutaneous indurations, some nodular others string like, over the forearms and feet, and minute periungueal infarcts 2 days later multiple inflammatory cords on the forearms, hands and feet and subungueal-splinter hemorrhage	TAO diagnosis 1 year later according to clinical manifestation and excluding other types of vasculitis	40 cigarettes per day	Ruling out vasculitis and cancer but there was no idea about the underlying cause of subungueal-splinter hemorrhage until the diagnosis of TAO	Heparin, steroids and vasodilators	No improvement during medical treatment but resolved later
4	1980	Rye et al (Washington, USA) <sup>75</sup>	1	57 years	Painful swallowing and an ulcer in the mucosa of left posterior hard plate or due to Necrotizing sialometaplasia	TAO diagnosis 6 years earlier and minor amputations	One pack cigarette daily	Mucosal biopsy and histology examination confirmed necrotizing sialometaplasia and showed arterial organized thrombus	Smoking cessation	Recovery

Table 8 Data summary of patients with TAO and lymphohematopoietic system involvement

No	Year	Authors	The number of patients	Age	Chief complaint	Duration of disease (amputation)	Smoking status	How to diagnose the current disease	Suggested treatment	The outcome of treatment
1	2016	Akbarin et al (Iran) <sup>76</sup>	26 (26 CBC and serum samples out of 37 documents and banked samples)	27–49 years	40±7 years	Unknown	Mean cigarette consumption was 397.77 packs per year (minimum 60 packs and maximum 1110 packs per year)	Anemia defined as Hgb <13.5 g/dL for males which could not be explained by anemia of chronic disease or iron deficiency according to several indices including MCV, MCH, LDH, ALT, AST	Unknown	Unknown
2	2010	Takaoka et al (Japan) <sup>77</sup>	1	46 years	One month history of sharp rest pain in right calf and ischemic ulcer between the third and fourth toes of his right foot and lymphadenopathy in bilateral inguinal region	TAO diagnosis according to clinical manifestation and angiography pattern of lower limbs	About 10 cigarettes per day for 25 years	Excision biopsy of left inguinal nodule Histology examination demonstrated hyperplasia of lymphoid follicles with massive infiltration of eosinophil without malignancy CBC demonstrated eosinophilia	Prednisolon 40 mg per day	The eosinophilia, the ulcer and rest pain of right foot improved quickly
3	1971	Ward et al (Colorado, USA) <sup>78</sup>	1 (1 out of 31 cases of anemia suffering from chronic disease)	Unknown	Unknown	Unknown	Unknown	Laboratory tests Low hematocrit, normal iron level, high iron saturation, increased bone marrow iron with normal erythropoietin	Unknown	Unknown



**Table 9** Data summary of patients with TAO and arthralgia or arthritis

No	Year	Authors	The number of patients	Age	Chief complaint	Duration of disease (Amputation)	Smoking status	How to diagnose the disease	Suggested treatment	The outcome of treatment
1	2003	Johnson et al (Texas, USA) <sup>79</sup>	1	46 years	3-week history of acute polyarthriti	TAO diagnosis was made at the time of admission for working up arthritis according to clinical manifestation of the extremities, excluding other types of vasculiti and angiography	Three packs per day for over 30 years	Physical exam Laboratory tests	Corticosteroid therapy	Improved arthritis but progressive digital ischemia after 1 month
2	1999	Pu�chal et al (France) <sup>80</sup>	11 (11 out of 83 TAO patients)	Unknown	Recurrent episodes of transient and migratory Arthralgia of large joints	TAO diagnosis 2–13 years earlier	Unknown	Physical examination Laboratory tests Osteoarticular radiographs	Unknown	Unknown
3	1981	Queneville et al (Canada) <sup>75</sup>	1	44 years	4-week history of severe acute articular and periarticular pain which was initially located to the MTP joints and rapidly spread to the small and large joints	TAO diagnosis one year later according to clinical manifestation and excluding other types of vasculiti	40 cigarettes per day	Ruling out vasculiti as underlying cause but there was no idea about the underlying cause of subungueal-splinter hemorrhage until the diagnosis of TAO	Unknown	Unknown

**Table 10** Data summary of a patient with TAO and ear involvement

No	Year	Authors	The number of patients	Age	Chief complaint	Duration of disease (amputation)	Smoking status	How to diagnose the disease	Suggested treatment	The outcome of treatment
1	1962	Kirikae et al (Japan) <sup>81</sup>	1	40 years	Suddenly fullness, roaring tinnitus, and hearing impairment and distortion of sound in the right ear due to basilar artery occlusion History of suboccipital pain	TAO diagnosis one year earlier according to clinical manifestation, angiography of upper and lower limbs and the diagnosis confirmed by histology examination of radial artery	He is a moderate smoker	Audiography Basivertebral angiography	Unknown	Unknown

## Discussion

The most challenging aspect of TAO management is its unknown etiology. Even its classification is challenging: it is usually viewed as a peripheral arterial disease rather than a type of vasculitis, and TAO patients are typically referred to angiologists or vascular surgeons as opposed to rheumatologists. This may be because of the unfavorable response of TAO to immunosuppressant medication and its favorable response to smoking cessation. Also, TAO is not known as a systemic disease and, in its diagnostic criteria, only the involvement of the small- and medium-sized arteries of the extremities is considered. Although Leo Buerger was the first to notice visceral arterial involvement in TAO in the first series of patients he evaluated, clinical manifestation of TAO in other organs is nonetheless known as an unusual or progressive form of TAO.

However, according to our systematic search, reports of the involvement of almost all organs have been made in relation to TAO. We also located several reports of TAO presentation in other organs before disease diagnosis, in which the involvement of the extremities presented after visceral involvement. Notably, the characteristics of the visceral arteries in several cases looked like the arteries of the extremities according to coronary angiography or aortography, including skip lesions and corkscrew collaterals. Also, in autopsies of TAO patients, the vascular involvement of multiple organs has been noted. In addition, in some studies, conservative, systemic medical treatment and smoking cessation have led to the recovery of the patient from the onset of visceral TAO.

On the other hand, TAO might be a systemic disease with a main clinical presentation in the extremities. For instance, approximately 30% of the TAO patients in the Fida et al study had abnormal urine analysis, although the patients were symptom-free.<sup>71</sup>

Moreover, reports of visceral involvement in TAO might be much more numerous than what we uncovered in the literature due to several reasons. One reason is that TAO is not of particular interest to many journals in the fields of angiology and rheumatology, and such case reports are not pursued for publication. Another reason may relate to the poor follow-up of TAO patients. According to our own experience, the main obstacle to follow-up is the mandatory admonition of smoking cessation. For this reason, TAO

patients may prefer to ignore the bearable symptoms or to change health care providers. In many cases, TAO patients do not know that other organs can be affected by TAO, as was seen in some studies in which the patients experienced years of postprandial pain or weight loss without any follow-up. In some TAO cases, when we called the patient for follow-up, the family reported that the patient had died after experiencing abdominal or chest pain at younger than 50 years of age. Whilst there were no autopsies, we cannot prove that they died of visceral TAO, but it remains a possibility.

Unfortunately, our search did not reveal any treatment modality for visceral TAO because most of the cases did not have long-term follow-up to evaluate further visceral episodes of the disease. However, according to the current data, smoking cessation seems to be very helpful in patients' recovery from visceral TAO. Also, more than 65% of the patients who received only medical treatment in the form of a combination of a vasodilator with anticoagulants showed improvement. Anticoagulants and anti-platelets without vasodilators led to an improvement in about 50% of the patients. Moreover, corticosteroids and immunosuppressants, but not anti-thrombotic or vasodilator treatments, did improve the skin and joint manifestations of the disease whilst aggravating the limb ischemia and, in a case of mesenteric ischemia, led to perforation of the bowel, followed by death.<sup>15,72,73,79</sup> In terms of invasive treatments, bypass surgery had more acceptable outcomes in comparison to endovascular procedures, including stenting. However, more clinical evidence and clinical trials are needed to determine better management of patients with visceral TAO.

## Conclusion

All in all, this study reveals five main points that should be noted:

1. If we maintain the belief that visceral involvement is an unusual manifestation of TAO and insist on localizing it to the extremities, we may be pursuing the wrong path in determining the etiopathology of the disease and appropriate treatment.
2. All patients with a diagnosis of TAO should be aware of the possible involvement of other organs along with the attendant warning signs, such as postprandial pain, unexplained weight loss, chest pain, any episodes of transient hemiparesis and cognitive and behavioral changes.
3. Early, systemic medical treatment of patients suffering from visceral TAO may lead to better outcomes and reduce the overall mortality rate.
4. Corticosteroid therapy and endovascular stenting are not recommended for managing visceral TAO.
5. More clinical evidence with long-term follow-up is needed to determine a treatment modality for visceral TAO.

## Disclosure

The authors declare that there are no conflicts of interest in this work.

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