

Homozygous Factor V Leiden Thrombophilia in a Patient With Histologically Confirmed Thromboangiitis Obliterans

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ABSTRACT: Thromboangiitis obliterans (TAO) is a vasculitis characterised by segmental occlusions of small to medium-sized arteries and superficial veins, and a curious predilection for young male smokers. The exact aetiology remains unknown. Current theories postulate it is an autoimmune endarteritis, triggered by some constituent of tobacco and occurring in genetically susceptible individuals. The disease can pose a diagnostic challenge, requiring a high degree of clinical suspicion, particularly in male smokers aged between 20–45 presenting with peripheral ischaemia. The fundamental principle of management is absolute tobacco abstinence. In this article, we report the case of a 27-year-old man who presented with infected, chronic wounds of his upper and lower extremities. He was initially treated with antibiotics and surgical debridement. Unfortunately he went on to develop a protracted course of complications due to poor wound healing ultimately leading to amputation of several digits. A diagnosis of TAO was suspected, and this was later confirmed histologically. Incidentally and of note, the patient was also found to be homozygous for factor V Leiden. An association between TAO and hypercoagulable states, specifically heterozygous factor V Leiden mutation, has been previously described. It is unclear if a synergistic effect between TAO and homozygosity for factor V Leiden may have contributed to the severity and unremitting nature of our patient's symptoms. We present this case in order to highlight the importance of early recognition of the condition and the need to offer comprehensive smoking cessation support in order to prevent amputation and other complications of poor wound healing.

KEYWORDS: thromboangiitis obliterans, buerger's disease, factor V Leiden

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Introduction

Thromboangiitis obliterans (TAO), also known as Buerger's disease, is a vasculitis characterised by multiple, segmental occlusions of small- to medium-sized arteries and superficial veins. TAO can be distinguished from the other vasculitides by its predilection for young males and a very strong association with smoking and tobacco use; the exact mechanisms for which have not yet been elucidated.

The diagnosis and treatment of TAO can be challenging. We report the case of a patient with homozygous factor V Leiden mutation and biopsy proven TAO and review the relevant literature. Although an association between TAO and hypercoagulable states has been previously suggested, there are no previous case reports linking homozygous factor V Leiden mutation and TAO.

Case Report

A 27-year-old Caucasian gentleman was referred to the plastic surgery outpatient clinic with a 7 month history of pain and swelling of his left middle toe. The cause of his symptoms was unclear, with the patient linking the episode to minor trauma. Initially, he had seen a chiropodist who diagnosed him with an in-grown toenail. The toenail was subsequently removed; however, his symptoms worsened. At this stage, he was noted to have subungual discolouration. A punch biopsy was performed

with histology demonstrating a pigmented keratinous disc, and he was subsequently referred to our service as a possible case of malignant melanoma.

He has no other significant past medical history and did not take any regular medication. He smoked approximately 10 cigarettes per day since aged 15.

Upon review in clinic, he was found to have an ulcerated area over the dorsum of his left middle toe with associated erythema and swelling, which was actively discharging pus but good peripheral pulses. He also reported a 6-week history of similar symptoms on his left index finger, over the dorsum of the proximal inter-phalangeal joint (PIPJ) which had appeared spontaneously. He had been treated with several courses of oral antibiotics by his general practitioner with no improvement. He was admitted acutely for intravenous antibiotics, surgical exploration and washout of both digits, and a biopsy of the left middle toe for microbiology and histology to rule out osteomyelitis and malignant melanoma. Initial biopsy of the nail bed excluded malignancy and instead showed acute inflammatory changes. The index finger defect was further debrided and closed with a local flap.

Following this initial surgical intervention, the patient went on to have a long and protracted clinical course from complications of poor wound healing and necrosis, with multiple hospital admissions over a 15-month period. He was





Figure 1. Clinical photograph showing ray amputation of the second and third toes, with a poorly healed resultant wound.

reviewed by the vascular team with full assessment of peripheral vasculature using ankle-brachial pressure index and computed tomography (CT) angiography which did not identify a specific cause for his necrotic digits. He developed osteomyelitis of both the left third toe and left index finger, which required amputation to prevent proximal spread of infection. A clinical diagnosis of TAO was suspected when he developed similar symptoms in the adjacent left second toe 2 months after initial presentation. Negative autoimmune, vasculitic and coagulopathy screening blood tests, including anti-neutrophil cytoplasm antibodies (ANCA), erythrocyte sedimentation rate, anti-cardiolipin antibodies, anti-thrombin, proteins C and S, supported the diagnosis. Genotyping for prothrombin mutations was negative; however, the patient was positive for homozygous factor V Leiden mutation. Verbal smoking cessation advice was reinforced frequently; however, the patient found complete abstinence difficult. This ultimately resulted in a Ray amputation of the second and third toes due continued non-healing (Figure 1). Following this, he underwent a short period of remission. Unfortunately due to ongoing use of tobacco, symptoms recurred in the contralateral and dominant right hand affecting his index and middle finger tips (Figure 2A and B). The right index finger became gangrenous and required amputation. During the procedure, a segment of digital artery was biopsied. Histopathologic analysis showed evidence of chronic inflammation with lymphocytic arteritis and thrombosis, confirming a diagnosis of TAO (Figure 3).



Figure 2. Clinical photographs showing the development (A) and progression (B) of digital ischaemia secondary to TAO.

Discussion

TAO is an inflammatory vascular disease that commonly affects small- and medium-sized arteries and superficial veins of the upper and lower limbs.^{1,2} The disease is found worldwide, although prevalence is higher in the Oriental, Middle Eastern and Southeast Asian population.^{2,3} The exact aetiology remains unknown; however, a peculiarly strong association with tobacco exposure has been established.¹ Smoking or tobacco consumption is a key factor in the initiation and progression of the disease. TAO occurs more commonly in young men, usually between the ages of 20-45 with a male-to-female ratio of 3:1. Incidence is believed to be increasing in women and has been attributed in part to the increasing prevalence of smoking amongst women.⁴

Although the exact aetiology of TAO remains unknown, current theories postulate that it is an autoimmune endarteritis, triggered by some constituent of tobacco and occurring in genetically susceptible individuals.³ Individuals with the disease exhibit higher levels of human leukocyte antigen (HLA) A9, A54 and B5, and lower levels of HLA-B12, suggesting a genetic component.^{3,4} These patients also show hypersensitivity to intradermally injected tobacco extracts and increased cellular sensitivity to types I and III collagen. Serum levels of antiendothelial cell antibodies, the presence of which is reported in various other vasculitides and connective tissue diseases, are also elevated in patients with TAO.⁴

Interestingly, genetic studies in our patient revealed the presence of a homozygous factor V Leiden mutation (HGVS-F5, NM_000130.4: c.1601G>A, NP_000121.2: p. Arg534Gln). An association between TAO and hypercoagulable states has been previously suggested. In the normal coagulation cascade, factor V is normally inhibited by activated protein C (APC) that acts to regulate the clotting process. In factor V Leiden thrombophilia, the variant factor V is resistant to APC, which increases the risk of abnormal clotting and deep venous thromboembolism (VTE).⁵ Although manifestation of VTE in factor V Leiden thrombophilia is variable, it has been reported^{6,7} that

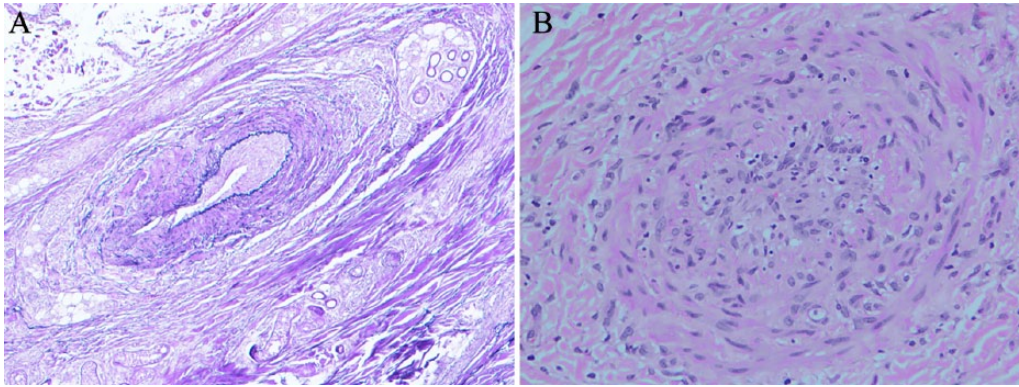


Figure 3. Histological appearance of biopsy tissue from the right index finger. (A) Epidermis with focal ulceration and a dermal acute on chronic inflammatory infiltrate surrounding adnexal structures; TAO is present with dermal fibrosis and background necrotic ulcer debris (40× magnification). (B) Fibrovascular tissue with chronic inflammation, lymphocytic arteritis and thrombosis (200× magnification).

homozygotes are twice as likely to develop VTE by the age of 33 compared with heterozygotes. The presence of heterozygotic mutations in prothrombotic factors in patients with TAO, namely factor V and prothrombin, has been investigated with conflicting results.^{8–11} A literature search did not identify any cases of homozygous factor V Leiden mutation associated with TAO. Nevertheless, it is possible the homozygous factor V Leiden mutation in our patient may have contributed to the severity, and unremitting nature of his disease. Other thrombophilic states including, hyperhomocysteinaemia and antiphospholipid syndrome, in the context of TAO have also been described.^{12,13} Further study is required to establish whether the formation of thrombotic occlusions in TAO is influenced by these hypercoagulable states or is simply due to the inflammatory process within the vessel wall.

There is a lack of consensus in the literature on the clinical diagnostic criteria for TAO.¹⁴ The most commonly mentioned include age at onset less than 45 years; current or recent history of tobacco use; presence of distal extremity ischaemia – indicated by claudication, pain and ulceration or gangrene; migratory superficial phlebitis; Raynaud's phenomenon; upper limb involvement and objective documentation of distal vaso-occlusive disease – indicated by angiographic studies or histopathology.

Biopsy and tissue sample, although not essential in securing a diagnosis, can help distinguish TAO from atherosclerosis and other forms of vasculitis. Three histopathologic phases of the disease have been described.¹⁵ In the acute phase, an occlusive inflammatory thrombus containing polymorphonuclear leukocytes, multinucleated giant cells and micro-abscesses develop in the distal circulation. In contrast to other systemic vasculitides, the internal elastic lamina appears relative spared. In the subacute phase, inflammatory cells persist and the thrombus becomes more organised. The chronic phase is characterised by fibrosis and an organised thrombus without the presence of inflammatory cells. The histopathology results for our patient were consistent with the subacute phase. Serological markers of autoimmune disease and a full coagulation screen should be performed to rule out alternative diagnoses.

At present, there is no specific treatment for TAO. The fundamental principle in its management is absolute tobacco abstinence. Disease activity closely parallels any form of tobacco consumption including nicotine replacement therapies. Patients with intractable nicotine dependence who continue to use tobacco are at great risk of amputation. Therefore, clinicians have a duty to educate and counsel their patients frequently about the importance of cessation as well as consider offering pharmacotherapeutic agents (bupropion or varenicline) to assist with abstinence.¹⁵ Despite the inflammatory nature of TAO, anti-inflammatory agents such as steroids have no proven benefit.³ Similarly, there is no clinical evidence to support the use of calcium channel blockers, vasodilators, thrombolytic agents or oral anticoagulants.¹⁶ The need for anticoagulation in the presence of concurrent prothrombotic state, such as in our patient, is less clear cut.⁵ The use of prostaglandins, however, specifically intravenous iloprost, has been shown to improve symptoms and reduce amputation rate.³ Bacterial or fungal infections should be treated empirically.

Similar to other forms of peripheral vascular disease, chronic poorly healing wounds are a common feature of TAO. It is therefore important for patients to avoid thermal, chemical or mechanical injury, for example, from ill-fitting footwear or from minor surgery to unaffected digits. Our patient's symptoms began following innocuous trauma and a subsequent removal of the nail plate.

Surgical management in established disease is limited, with vascular bypass rarely successful.¹⁴ On account of the aforementioned, inevitable wound-healing problems, it has been suggested¹⁶ that definitive amputation and reconstruction of a digit or limb in non-infected cases should be postponed until after the patient ceases tobacco use and clearly demarcated dry gangrene is established. For similar reasons, minimal judicious surgical debridement should be performed if clinically indicated.

Conclusions

A plastic surgeon may very well be the first clinician a patient with gangrene of the fingers secondary to TAO encounters. The disease

can pose a diagnostic challenge, and a high degree of suspicion is required if a young male smoker presents with evidence of peripheral ischaemia. We present this case to highlight the importance of early recognition of the condition and the need to offer comprehensive smoking cessation support in order to prevent amputations and other complications of poor wound healing.

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Author Contributions

MM: involved in the clinical care of the patient; wrote the draft manuscript; collected and assembled clinical photographs; performed a literature review; and contributed to critical revision of the final manuscript and approval of the version to be published. TD: involved in the clinical care of the patient; review and editing of the draft manuscript; and contributed to critical revision of the final manuscript and approval of the version to be published. ZMJ: involved in the clinical care of the patient; identified the case; obtained informed consent; review and editing of the draft manuscript; and contributed to critical revision of the final manuscript and approval of the version to be published. ISW: involved in the clinical care of the patient; identified the case; obtained informed consent; and contributed to critical revision of the final manuscript and approval of the version to be published.

Informed Consent

Written informed consent was obtained from our patient for publication of this case report and any accompanying images.

A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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