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Case Report

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# Rare Case of Buerger's Disease with Acute Fulminant Progression to Digital Ischaemia Despite Aggressive Medical Treatment

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## 1. Abstract

Buerger's disease, also known as thromboangiitis obliterans (TAO), is a non-atherosclerotic, segmental inflammatory disease affecting small to medium-sized arteries and veins in the limbs. It is a rare disease seen mostly in young male smokers below 45 years of age. Disease course is typically gradual, progressing from claudication symptoms to rest pain eventually ischemic ulcers and gangrene. It is rare for patients to present with ischemic pain with rapid worsening in days.

This is an interesting case of a 52-year-old male with no known past medical history who presented with digital ischemic rest pain. Initial investigations revealed mildly elevated inflammatory markers, while imaging studies showed thrombosis of bilateral radial and ulnar arteries, with dampened photoplethysmography. He was assessed to be unsuitable for endovascular intervention, consequently was treated medically with anticoagulants, statin, and prostaglandin analogue. He subsequently showed clinical improvement, with no compromise of his hand circulation, and was able to return to work. We report a rare clinical presentation of TAO that may be of diagnostic clinical challenge at the onset. Asians may be affected above the age of 50 years with acute fulminant progression to ischaemia and digital gangrene despite of aggressive medical treatment.

## 2. Introduction

Buerger's disease, also known as thromboangiitis obliterans (TAO), is a non-atherosclerotic, segmental inflammatory disease that most commonly affects the small and medium sized arteries and veins in the upper and lower extremities. TAO has a strong association with young male smokers, classically occurring in patients between 20 and 50 years of age. We describe a 52-year-old Chinese male with TAO with acute fulminant progression in spite of aggressive medical management with antiplatelet, anticoagulation and vasodilators.

## 3. Case Report

A 52 year-old male (of Chinese heritage) presented to the Emergency Department of an Acute Restructured Hospital in Central Singapore for numbness and discoloration over bilateral fingertips. The numbness first started over the right middle finger, spreading over the course of one week to involve the rest of his fingers on both hands. The patient then noticed purple discolouration of his skin over his fingers, associated with pain and reduced sensation. A week before he presented to the emergency department, he sought treatment at a Primary Care Physician, and was prescribed Vitamin B Complex to address his numbness. As the symptoms were refractory to initial treatment, the patient sought consult at Emergency Department.

Upon further history, there was no presence of Reynaud's phenomenon over the fingertips. There were no complaints of fever, bodily rashes, or alopecia. There were no reports of swallowing difficulty or orogenital ulcers. There were no constitutional symptoms during the recent months. Overall, this is the first occurrence of symptoms for the patient. His cigarette smoking consumption is about ten pack-years. He has no family history of cardiovascular or peripheral vascular disease.

## 4. Physical Examination

General inspection showed no rashes or scarring alopecia. There were no mouth ulcers, no parotid gland enlargement, and no lymphadenopathies. The carotid pulses were well felt, and there was no carotid bruits.

On closer inspection of the patient's hands, duskiness was seen on all fingers, up to the extent demarcated by the proximal interphalangeal joint crease (Figure 1). The capillary refill time on all fingers was delayed at four seconds. There were no Gottron's papules or palmar hyperkeratosis. There were no nail fold changes or periungual erythema. Bilateral radial and ulnar pulses were well felt. Joint examination was normal. His femoral, popliteal, posterior tibialis and dorsalis pedis pulses were well-felt bilaterally. Systemic examination was normal.

## 5. Investigations

Initial blood workup showed leucocytosis, thrombocytosis, mildly elevated C-reactive protein and erythrocyte sedimentation rate (Table 1). Other serological tests for immunological markers and auto-antibodies were normal or negative. Virology markers for coronavirus disease-2019 (COVID-19), hepatitis viruses and Human Immunodeficiency Virus (HIV) were negative. Haematological markers for hypercoagulable state were also negative (Figure 1).

Arterial duplex scans of the right hand showed thrombosis of the distal radial artery from 1cm below the wrist crease and the ulnar artery from 3.5cm above the wrist crease. The right palmar arch was occluded. Arterial duplex of the left hand showed thrombosis of the distal radial artery from the wrist crease and ulnar artery from 3cm above the wrist crease (Figure 2). Dampened photoplethysmography (PPG) signals were recorded from the right first to fifth digits, and the first, second, fourth and fifth digits on the left. PPG signal was absent from the left third digit. Digit brachial pressure ratios were abnormal for all digits. Lower limb toe brachial pressure indices were normal bilaterally (Figure 3).

Computed tomography (CT) aortogram and Transthoracic Echocardiogram (TTE) performed did not reveal any thrombus or intra-cardiac shunt. The Vascular Surgeons and Interventional Radiologists opined that the patient was deemed not a candidate for revascularization therapy, as the disease was bilateral, and the involved vessels were too small in calibre.

**Table 1:** Investigations

| | |
|---|---|
| **Full Blood Count** | |
| Hemoglobin (g/dL) | 14.2 |
| White Blood Cells (x10^9/L) | 14.7 |
| Platelets (x10^9/L) | 414 |
| **Inflammatory Markers** | |
| C-Reactive Protein (mg/L) | 13.8 (H) |
| Erythrocyte Sedimentation Rate (mm/hr) | 32 (H) |
| **Renal Panel and Extended Electrolytes** | |
| Urea, Serum (mmol/L) | 4.4 |
| Creatinine (umol/L) | 80 |
| Serum Sodium (mmol/L) | 138 |
| Serum Potassium (mmol/L) | 3.8 |
| Serum Magnesium (mmol/L) | 0.9 |
| Serum Adjusted Calcium (mmol/L) | 2.36 |
| Serum Phosphate (mmol/L) | 1.2 |
| **Coagulation Panel** | |
| INR | 1.1 |
| PT (secs) | 13.5 |
| APTT(secs) | 32.5 |
| Creatinine Kinase (U/L) | 107 |
| **Metabolic Screen** | |
| HbA1c (%) | 5.7 |
| Total Cholesterol (mmol/L) | 4.2 |
| Triglycerides (mmol/L) | 1.2 |
| HDL Cholesterol (mmol/L) | 0.9 |
| LDL (Calculated) (mmol/L) | 2.7 |
| **Anti-phospholipid Syndrome Screening** | |
| Lupus Anticoagulant | Absent |
| Anti-cardiolipin (MPL Units) | <20 |
| Anti-B2 Glycoprotein (RU/mL) | 2 |
| Anti-Cardiolipin (ACA) IgM (MPL Units) | <20 |
| Anti-Cardiolipin (ACA) IgG (GPL Units) | <20 |
| **Pro-Thrombotic Screen** | |
| Anti-Thrombin III (80-130%) | 110 |
| Homocysteine (umol/L) | 8 |
| Protein C Activity (70 -150%) | 119 |
| Protein S Activity (65 – 130%) | 99 |
| **Auto-Immune Screen** | |
| C3 Complement (g/L) | 1.57 |
| C4 Complement (g/L) | 0.31 |
| Rheumatoid Factor (0 – 20 RU/mL) | 102 (H) |
| ANA-Immunofluorescen (Titre) | 80 |
| Anti-IFA (Pattern) | Nucleolar |
| Anti-CCP (0.0 – 20.0 Units) | <20.0 |
| Anti-SCL70 (0 – 20 RU/mL) | < 20 |
| Anti-CENP A ș | 1 |
| Anti-CENP B | 1 |
| Anti-RP11 | 5 |

| | |
|---|---|
| Anti-RP155 | 4 |
| Anti-Fibrillarin | 11 |
| Anti-Nor90 | 3 |
| Anti-TH/TO | 5 |
| Anti-PDGFR | 2 |
| Creatine Kinase (50 – 350 U/L) | 107 |
| Anti-Nuclear Cytoplasmic Antibody | Negative |
| **Virology** | |
| Anti-HBc Total | Non-reactive |
| HBsAg | Non-reactive |
| Anti-HCV | Non-reactive |
| HIV Ag-Ab Screen | Non-reactive |
| SARS - CoV2 | Not detected |

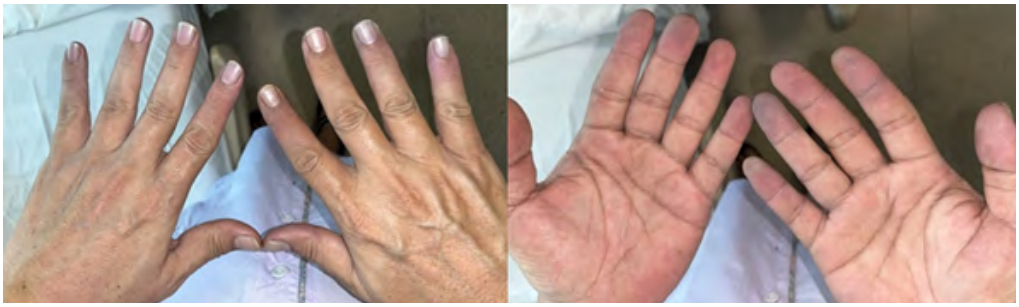

**Figure 1:** Clinical photograph of patient's hands depicting dusky discolouration involving all fingertips

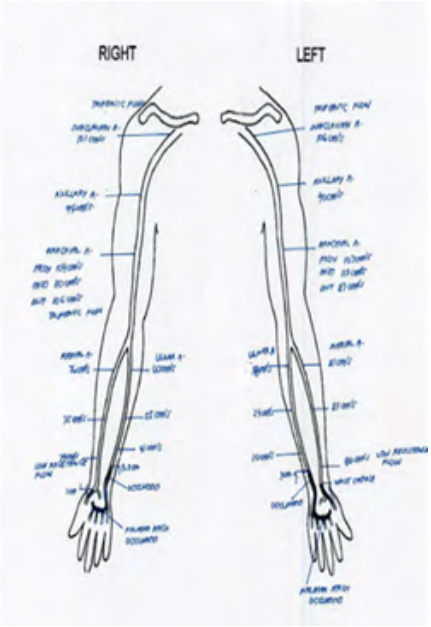


**Figure 2:** Arterial duplex study

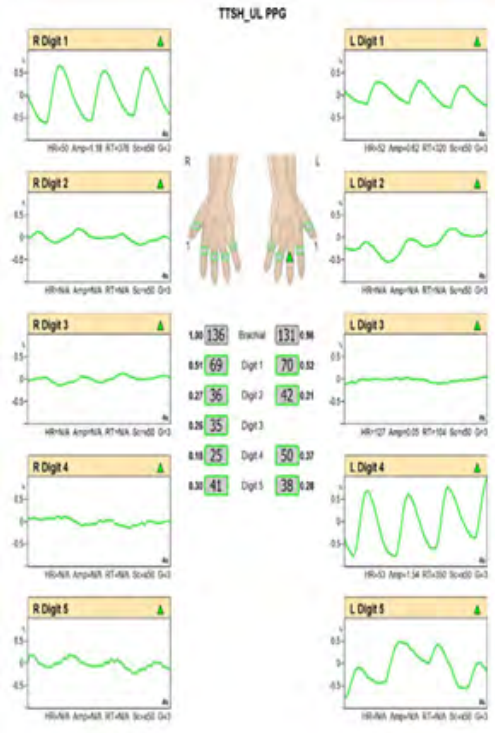


**Figure 3:** Upper limb photo plethysmography

## 6. Treatment

The patient was empirically treated with Aspirin 100 mg once daily, Atorvastatin 40 mg once daily, Nifedipine LA (long-acting formulation) 30 mg twice daily, Pentoxifylline 400 mg thrice a day, and Rivaroxaban 20 mg once daily. Despite medical therapy, the patient's condition started to worsen, with dusky discoloration extending proximally to the extent of the interphalangeal crease.

Rheumatology was consulted, and assessed that there was no suggestion of vasculitis or any rheumatological disorder, as well as suggested initiation of Epoprostenol (a prostaglandin analogue).

The patient received intravenous Epoprostenol for three days (at a rate of 8 mcg/hr). Subsequently, there was note of clinical improvement: increased temperature to distal digits, and dissipation of discoloration of the fingers. He agreed on complete cessation of cigarette smoking after Smoking Cessation Pharmacist counselling. After two weeks of inpatient stay, the patient was discharged, with Rivaroxaban dose reduced to 2.5mg twice a day.

Eight weeks after discharge, the patient was seen at the Vascular Medicine Clinic. There was resolution of digital ischemia, and with full recovery of function. He is given continuation of medical therapy and repeat Clinic follow-up.

## 7. Discussion

TAO classically occurrs in patients between 20 and 50 years of age, with a male-to-female ratio of 3:1 [1]. The disease incidence is more prevalent in the Middle East and parts of Far East Asia compared to Western Europe [2]. The traditional diagnosis of TAO is based on five criteria (smoking history, onset before the age of 50 years, infra-popliteal arterial occlusive disease, either upper limb involvement or phlebitis migrans, and absence of atherosclerotic risk factors other than smoking) [3]. As there is no specific diagnostic test, and an absence of positive serologic markers, the confidence in arriving at TAO as a diagnosis by fulfilling these five criteria may be used, but has not been universally accepted. The angiographic findings of multiple small and medium arterial occlusions with corkscrew collaterals in Buerger's disease are helpful, but not pathognomonic [4].

Although smoking cessation is universally accepted as a cornerstone in the management of TAO, there is no universal consensus on the most optimal medical or surgical treatment for the disease.

Medical treatment such as antiplatelets, anticoagulants, thrombolytics, vasodilators, Pentoxifylline, Cilostazol, Prostaglandins and Endothelin-antagonists can be used to treat a patient with TAO. Endovascular revascularization, intra-arterial thrombolysis, and even mechanical thrombectomy are amongst the many surgical approaches being used worldwide for the treatment of TAO.

This case presents an unusual presentation of Buerger's disease. Classically, this disease presents in patients who are less than 45 years old, and most diagnostic criteria have an age limit of 50 years [5]. This patient's age on presentation made the initial impression of Buerger's disease less likely. However, a study in Korea published has shown that the peak incidence of Buerger's disease occurred in patients above the age of 50, compared to France, where the peak incidence occurred in patients below the age of 50 [6,7]. The difference in age incidence between Western and East Asian populations should prompt clinicians to consider the diagnosis of Buerger's disease even if patients are above the age of 50.

Buerger's disease is typically a slow and progressive disease. A retrospective multicentre study of outcomes of 224 patients with TAO showed that the five-year amputation-free survival from date of diagnosis was 85% [8]. Major amputation is usually required after a period of remission in patients who continue to smoke. Most patients underwent major amputation or minor amputation only 10 to 15 years after disease onset. This patient presented with claudication symptoms, which progressed to acute limb ischemia rapidly over days, suggestive of a fulminant form of TAO in spite of aggressive medical treatment.

Elevation in homocysteine levels has also been proposed in a case series report to increase amputation rates of patients with TAO [9]. However, our patient's rapid progression of symptoms, despite normal levels of homocysteine, cannot be explained by the above mechanism. Studies have shown that acute phase reactants and autoimmune serologies are typically not elevated or negative for patients with Buerger's disease. Elevation of acute phase reactants, leucocytosis with neutrophilia and thrombocytosis in this patient might suggest an underlying infection. Studies from Mayo Clinic have proposed an infectious aetiology to TAO [10]. Another study in Japan found oral bacteria (periodontal) DNA in the arterial specimens of Buerger's disease in 93% of cases, by demonstrating (via electron microscopy) platelet engulfment of oral bacteria and subsequent transport and accumulation of platelet aggregated mass in the terminal vessels [11]. Although we did not conduct periodontal DNA sampling in this patient, an acute infection could rapidly worsen thrombosis of his upper limb vessels. This patient's distal site of disease and small-calibre of vessels prevented the use of endovascular revascularization techniques. Medical treatment with antiplatelet and anticoagulation could not even prevent the progression of the disease in this patient.

## 8. Conclusion

Buerger's disease, or Thromboangiitis Obliterans (TAO), is a rare condition that presents a diagnostic challenge to many clinicians. Asians may be affected above the age of 50 years with acute fulminant progression to ischaemia and digital gangrene in spite of aggressive medical treatment.

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