CASE REPORT

The prolonged clotting time in two female patients with thromboangiitis obliterans

Yiping Dang,¹ Yin Xia,² Yiqing Li,¹ DannyCW Yu³¹Department of Vascular Surgery, Union Hospital, Wuhan, China²Department of General Surgery, Fuzhou General Hospital, Fuzhou, China³Department of Newborn Medicine, Brigham and Women's Hospital, Boston, Massachusetts, USA**Correspondence to**
DannyCW Yu,
dannychenwei@gmail.com**SUMMARY**

Thromboangiitis obliterans (TAO), also known as Buerger's disease, is segmental non-atherosclerotic inflammatory disease, which affects the small and medium-sized peripheral arteries, veins and nerves of young adult smokers. The paper reports two TAO female patients, 26-year-old and 42-year-old, with prolonged clotting time. We compared 13 male patients and 2 female patients with TAO. The prothrombin time (PT), activated partial thromboplastin time (APTT) and thrombin time (TT) were normal in the male patients, whereas the clotting times were prolonged in the female patients. Coagulation tests including PT, APTT and TT evaluation could be the potential markers to female patients with TAO.

BACKGROUND

Thromboangiitis obliterans (TAO) is a relatively rare disease of peripheral blood vessels affecting small-sized and medium-sized arteries and veins.¹ Although TAO is observed worldwide, it has been reported as being more prevalent in the Middle East and Far East.² Smoking is considered as a precipitating factor of TAO, but the essential mechanism remains unclear. The therapeutic options on TAO are limited, since the aetiology and pathogenesis of TAO remains largely unknown. Evidences have shown that TAO typically affects young male smokers, but the prevalence in women is rising because of tobacco consumption.¹ In addition to other peripheral arterial diseases, although the younger patients with TAO are not as severely limited, the severe mutilation is frequently seen after major amputations. Nowadays, vascular surgery is still the most common way to improve blood flow to the affected extremity of TAO.

Previous studies showed that the lower clot permeability and prolonged clot lysis were associated with the progression of TAO patients.³ However, the exacerbation of TAO has also been indicated that associated with the platelet activation.⁴ These studies did not compare the gender difference. The present study was therefore to investigate the sex-related differences in coagulant tests in the patients with TAO.

CASE PRESENTATION

All patients were for the first time attending the vascular clinics and were then scheduled for blood sample collection. This report comprised 15 patients including 13 male and 2 female patients with TAO and all clinical tests were monitored for

a week. The two female patients were the only females with TAO in this study.

Patients were recruited from Fuzhou General Hospital of Nanjing Military Command and Wuhan Union Hospital, China. Symptoms and signs of critical limb ischaemia including rest pain, ulcerations and intermittent claudication were recorded if the patients experienced pain within 10 min. All patients in this report were diagnosed TAO by Philips iU22 xMATRIX ultrasound system and/or SOMATOM Definition 128 Slice, Siemens (figure 1). All patients involved in this study gave informed consent and the procedures followed were approved by institutional ethics committee of Wuhan Union Hospital, China. Except coagulation test, no other abnormal values from blood test including systolic blood pressure, albumin, total protein, alkaline phosphatase (ALP), alanine transaminase (ALT), aspartate aminotransferase (AST), γ -glutamyltransferase (γ -GT), total bilirubin, direct bilirubin, mean corpuscular volume, mean corpuscular haemoglobin (MCH), MCH concentration, platelets, neutrophil and monocyte counts were found in the male and the female patients with TAO. The female patients had statistical significantly higher levels of prothrombin time (PT) (men: 11.52 ± 1.24 , women: 16.75 ± 3.32 , $p=0.001$), APTT (men: 28.96 ± 6.91 , women: 47.70 ± 5.94 , $p=0.003$) and thrombin time (TT) (men: 15.45 ± 6.36 , women: 59.20 ± 22.06 , $p<0.001$) compared with male patients (table 1). Because of the two female patients with abnormal higher levels of PT, APTT and TT, we treated them with a dose of 2.5 mg of oral vitamin K. The values of PT, APTT and TT were reinstated to the normal range after a week. No statistically significant differences were found in the coagulation tests between male and female patients with TAO, after the patients received vitamin K treatment.

INVESTIGATIONS

Two samples of 20 ml non-fasting venous blood without taking any medication were taken into vacuum tubes containing EDTA or sodium citrate for haematological and biochemical analysis, respectively. Plasma was separated by double centrifugation at 800 g for 10 min; 1600 g for 10 min and the aliquots were immediately frozen at -70°C . Plasma biochemical analysis was undertaken by Olympus AU5400 Chemistry System. Fibrinogen, PT, activated partial thromboplastin time (APTT) and TT were measured by STA-R Evolution. A complete blood count was analysed by Sysmex XT-1800i Automated Hematology Analyzer. All data are presented as mean values $\pm$ SD. Statistical analysis into the differences between male and

To cite: Dang Y, Xia Y, Li Y, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2013-009427

Figure 1 CTA showing the patient suffers from thromboangiitis obliterans in both lower extremities. Infrapopliteal arteries showing the multiple occlusions and all arteries are free of atherosclerosis. The arrows show the corkscrew-shaped collateral vessels around the areas of occlusion. CTA, computed tomography angiography.

female potential risk factors was conducted by covariance (ANCOVA) with age as a covariate using SPSS V20 software (IBM, USA). Data were considered statistically significant at the level of $p < 0.05$.

DISCUSSION

The present study investigated several potential circulating risk factors of TAO in young adults with smoking history in the Chinese hospital-based patients. Although tobacco consumption is the most important risk factor, TAO may also develop as a result of chewing marijuana. Our results indicate that two female patients with TAO had prolonged time of coagulation test including PT, APTT and TT.

The expression levels of platelet microparticles (PMPs) reflect the conditions of platelet apoptosis and activation, and platelet aggregability could be modified in smokers,⁵ suggesting that coagulation function might be highly associated with occurrence

of TAO. PMPs levels are related with the severity of several pathological conditions such as the heparin-induced thrombocytopenia, chronic renal failure and cardiovascular diseases including peripheral vascular disease.⁶ Previous studies showed that PMP levels were significantly higher in patients with acute phase of TAO than in patients with stable phase of TAO.⁴ Furthermore, the lower clotting ability and extended clot lysis have been shown in TAO patients.³ Our results show that the prolonged time of coagulation tests including PT, APTT and TT were only observed in the female patients with TAO. Therefore, further investigation is necessary to clarify the gender difference associated with TAO in clinical outcomes.

The deficiencies associated with clotting factors principally reveal an impaired hepatic synthetic function. The expression levels of fibrinogen, PT, APTT, TT and platelet count could provide a measure for the severity of liver disease and may act as a baseline to screen blood product replacement. The concentration of fibrinogen in plasma is also one of the determining factors of blood viscosity. Prolonged PT and APTT accord with the progression of liver disease and TT is prolonged as a result of hypofibrinogenemia or dysfibrinogenemia.⁷

Our findings indicate that the two female patients with TAO had prolonged PT, APTT and TT, whereas the observation is not seen in the male patients. Nevertheless, our finding showed that the liver function test including fibrinogen, albumin, total protein, ALP, ALT, AST, γ -GT, total bilirubin and direct bilirubin were in the normal reference ranges in all patients. We herein suggest that a novel clue for the first time that the gender-related differences and coagulation dysfunction, but not liver disease, may play an important role in the unsolved mechanism of TAO in the young smoking population.

Table 1 Characteristics of the 15 patients with TAO and differences by gender

Variables (reference values)	Men (n=13)	Women (n=2)	p Values
Age (years)	36.8±6.4	34.0±11.3	0.608
PT (10–16; seconds)	11.52±1.24	16.75±3.32	0.001**
APTT (23.5–43.5; seconds)	28.96±6.91	47.70±5.94	0.003**
TT (14–20; seconds)	15.45±6.36	59.20±22.06	<0.001***
Fibrinogen (2–4; g/l)	3.97±0.93	3.00±0.44	0.177

** $p < 0.01$, *** $p < 0.001$ were represented in the table.

APTT, activated partial thromboplastin time; PT, prothrombin time; TAO, thromboangiitis obliterans; TT, thrombin time.

Learning points

- ▶ Thromboangiitis obliterans (TAO) also known as Buerger's disease is a rare inflammatory peripheral vascular disease, which affects the small-sized and medium-sized arteries, veins and nerves of the extremities.
- ▶ The disease is characteristically present in young smokers or marijuana users with an age of around 45 years.
- ▶ The function of coagulation tests including platelet microparticles, clotting ability, prothrombin time, activated partial thromboplastin time and thrombin time could be the potential markers to evaluate the progression of patients with TAO.

Contributors Yiping Dang undertook statistical analysis and drafted the manuscript, Yin Xia collected the patients' data, Yiqing Li co-directed the work, DannyCW Yu designed and directed the study. All authors read and approved the final manuscript.

Competing interests None.

Funding This study was supported by the China Scholarship Council #2011616098 and by the Brigham and Women's Hospital Biomedical Research Institute.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Piazza G, Creager MA. Thromboangiitis obliterans. *Circulation* 2010;121:1858–61.
- 2 Malecki R, Zdrojowy K, Adamiec R. Thromboangiitis obliterans in the 21st century—a new face of disease. *Atherosclerosis* 2009;206:328–34.
- 3 Undas A, Nowakowski T, Ciesla-Dul M, *et al*. Abnormal plasma fibrin clot characteristics are associated with worse clinical outcome in patients with peripheral arterial disease and thromboangiitis obliterans. *Atherosclerosis* 2011;215:481–6.
- 4 Darnige L, Helley D, Fischer AM, *et al*. Platelet microparticle levels: a biomarker of thromboangiitis obliterans (Buerger's disease) exacerbation. *J Cell Mol Med* 2010;14:449–51.
- 5 Fusegawa Y, Handa S. Platelet aggregation induced by ADP or epinephrine is enhanced in habitual smokers. *Thromb Res* 2000;97:287–95.
- 6 Tan KT, Tayebjee MH, Lynd C, *et al*. Platelet microparticles and soluble P selectin in peripheral artery disease: relationship to extent of disease and platelet activation markers. *Ann Med* 2005;37:61–6.
- 7 Rapaport SI. Coagulation problems in liver disease. *Blood Coagul Fibrinolysis* 2000;11(Suppl 1):S69–74.

Copyright 2013 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow