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Protein C Deficiency with Recurrent Deep Vein Thrombosis Complicated with Post Thrombotic Syndrome – A Case Report and Mini Review

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Abstract

Protein C is a vitamin K dependent glycoprotein produced by the liver. Protein C acts as a naturally occurring anticoagulant and its deficiency, predisposes the individual to a state of thrombosis, particularly venous thromboembolism. Post-thrombotic syndrome (PTS) is a chronic venous insufficiency manifestation following an episode of deep-vein thrombosis (DVT). We presented a case of 56-year old Malay man who was diagnosed with Protein C deficiency and presented with recurrent DVT complicated with PTS.

Keywords
Protein C deficiency, Post-thrombotic syndrome

Introduction

Activated protein C (APC) is a serine protease derived from its inactive precursor, protein C (PC). Protein C is a vitamin K-dependent plasma protein zymogen that plays critical roles in human thrombosis and hemostasis regulation. APC acts as a potent natural anticoagulant by inactivating factors Va and VIIIa [1]. Activated Protein C cleaves and inhibits membrane-bound factor Va and factor VIIIa, resulting in targeted and effective coagulation pathway downregulation. In these processes, Protein S and intact factor V (FV) serve as cofactors to activated Protein C [2]. Protein C deficiency is a rare autosomal dominant condition with a mild form affecting 1 in 200 to 1 in 500 individuals. Meanwhile, the severe form of Protein C deficiency has a frequency of 1 in 500,000 to 750,000 individuals [3]. Patients with reduced plasma levels Protein C are linked to an increased risk of venous thromboembolism (VTE) or disseminated intravascular coagulation [1, 4].

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The post-thrombotic syndrome (PTS) is a common consequence of deep venous thrombosis (DVT). Clinically, PTS is distinguished by persistent, chronic pain, swelling, and other symptoms in the affected limb. PTS is burdensome and expensive due to its prevalence, severity, and chronic nature [5].

We described a case of recurrent DVT which is associated with PTS in a patient with Protein C deficiency. The aim of this report is to share our experience managing a rare case that presented to our hospital.

Case illustration

In this case report, we present a 56-year-old Malay gentleman with background history of type II diabetes mellitus, who experienced recurrent left lower limb DVT. The first episode of DVT started in year 2000 at the age of 34-year-old without any precipitating factor. There was no family history of thromboembolism in the family. During this episode, the physician started him on warfarin for 6 months duration. After stopping the warfarin, DVT recurred in 2001 and since then he was started on lifelong warfarin. Subsequent episodes of DVT were in 2004 and 2009 due to poor compliance, and he was treated in nearby hospital. In 2012, he was brought to our hospital after he involved in motor vehicle accident (MVA) and the warfarin was stopped because he experienced scrotal hematoma. Then, he developed extensive lower limb DVT due to poor ambulation post MVA. He was then started on heparin. In view of recurrent history of DVT and no thrombophilia study was done, we proceed with lupus anticoagulant (LA), anti-β_2 glycoprotein, anti-cardiolipin, protein C, protein S and anti-thrombin tests (Table 1). He was diagnosed to have protein C deficiency and was discharge well after few weeks with warfarin.

Table 1: Thrombophilia work-up in 2012

Parameters	Value	Normal value
Protein C activity	23.7%	70 – 140%
Protein S activity	116.0%	60 – 150%
Free protein S antigen	79.3%	Male: 72.2 – 123.3%
		Female: 57.6 – 112.5%
Antithrombin III	82.9%	83 – 128%
FVII assay	95.2%	50 – 190%
Lupus anticoagulant (LA)	Not detected	
Anti-β2 glycoprotein	Negative	
Anti-cardiolipin	IgG <10 GPL units	<10 GPL U/ml
	IgM < 7 MPL units	< 7 MPL U/ml

He again presented to us in November 2022 with a complaint of left lower limb pain and redness for three days. There was a history of wet cupping and massage over the left lower leg two days prior to the symptoms. His left lower limb was swollen, red, and warm, otherwise, no ulcer or bullous lesions were seen (Figure 1). The latest coagulation profile is shown in Table 2.

Table 2: Coagulation profile

Coagulation profile	Values	Normal Range
Prothrombin time	52.0 seconds	12.6 – 15.7 seconds
Activated prothrombin time (aPTT)	90.5 seconds	30.0 – 45.8 seconds
International normalized ratio (INR)	4.09	0.86 – 1.14

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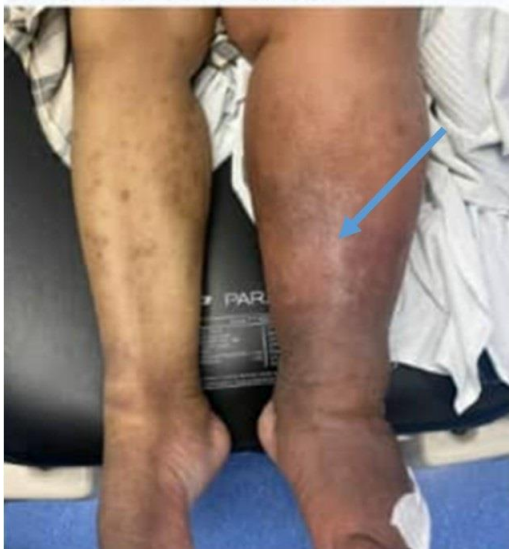

Figure 1. Left lower limb post-thrombotic syndrome

Urgent ultrasound of the left lower limb was performed and reported as persistent thrombosis over the left common femoral vein with left leg cellulitis. He was diagnosed to have PTS with acute left leg cellulitis in sepsis and over warfarinization. The warfarin was temporarily stopped and he was given intravenous antibiotic. He was discharged well after 2 weeks with warfarin.

Discussion

Protein C deficiency is a genetic or acquired risk factor for thrombophilia, with symptoms ranging from venous thromboembolism to purpura fulminant and disseminated intravascular coagulation, which can be fatal [4]. Protein C is a vitamin K-dependent plasma protein zymogen that plays critical roles in human thrombosis and hemostasis regulation [1]. Activated Protein C cleaves and inhibits membrane-bound factor Va and factor VIIIa, resulting in targeted and effective coagulation pathway downregulation. In these processes, Protein S and intact factor V (FV) serve as cofactors to activated Protein C [2].

We did not proceed with molecular test for this patient due to budget constrain. Griffin et al. described low Protein C antigen levels in a family with a history of recurrent thrombosis in 1981 [6]. Protein C deficiencies are autosomal dominant diseases that are usually caused by heterozygous mutations [7]. Although severe Protein C deficiency (homozygous or compound heterozygous variants) is exceedingly rare (1 in 500,000 to 1 in 750,000 births), partial deficiencies (heterozygous forms) are far more common (1 in 200 to 1 in 500) [4]. Heterozygous Protein C deficiency is inherited by autosomal dominant means, and it affects approximately 0.29% of the Chinese population [8]

Caspers et al. discovered that Protein C deficiencies are produced by similar mutation patterns, with missense mutations being the most common, followed by nonsense mutations, splice-site mutations, small duplications/insertions/deletions, and large deletions [9]. The thrombosis symptom was observed and reported in a family with missense mutations in the Protein C genes, p.Asp297His (c.889G>C) and p.Val420Leu (c.1258G>C) [10]. Gly197 is required for the activation of thrombomodulin cofactor-dependent Protein C by thrombin. It helps thrombin recognise Protein C in the presence of thrombomodulin but hinders it in the absence of the cofactor [11].

In a Chinese Protein C deficiency pedigree, a homozygous Pro275Ser mutation was discovered. Impaired mutant Protein C secretion could be the molecular mechanism of Protein C deficiency induced by the Pro275Ser mutation [12]. A total of 15 distinct causal mutations were discovered, with the Arg147Trp

substitution being the most common in the Chinese population at 43.5% [8]. According to Ding et al., approximately 50.0% of patients with recurrent thrombosis had more than one heterozygous mutation in the Protein C gene alone or in combination with the Protein S gene [8].

Acquired Protein C deficiency can occur as a result of warfarin or other vitamin K antagonist therapy, liver disease, uraemia, septicaemia, following plasma exchange, in cancer patients receiving certain types of chemotherapy, and dilution with crystalloid solutions [13].

Protein C levels are generally low in neonates (approximately 20–30% of adult values) and grow with maturity, reaching adult levels by the age of 11-16 years [13]. In women, mean Protein C activity increased with age. Meanwhile, mean Protein C levels in men increased with age until the age of 49 but then declined. Protein C levels are lower in young individuals, particularly men, than in middle-aged or elderly adults [13, 14].

Reduced plasma levels of acquired Protein C or Protein C are linked to an increased risk of venous thromboembolism (VTE) [1]. Almost all patients with Protein C deficiency had lower extremity DVT, with only one having a pulmonary embolism (PE). Complex Protein C antigen genotypes, alone or in combination with Protein S deficiency, are the primary cause of an increased risk of recurrent VTE [8].

A common side effect of DVT is PTS. PTS is clinically defined as chronic, persistent pain, edoema, and other symptoms in the affected limb [5]. Within 1-2 years of DVT, one-third to half of the patients will develop PTS [15, 16]. PTS affects more than one-third of women with DVT, with 5-10% developing severe PTS, which can present as venous ulcers. The main risk factors for PTS are persistent leg symptoms one month after acute DVT, anatomically extensive DVT, recurrent ipsilateral DVT, poor initial anticoagulation quality for DVT treatment, increasing body mass index (BMI), and older age [15, 17]. PTS affected 82% of patients treated after their first acute DVT. The highest likelihood of developing severe PTS was observed following four-level DVT and lower leg DVT [18]. If anticoagulation is insufficient (e.g., subtherapeutic INR > 50% time) during the first three months of treatment of vitamin K antagonist medication, the risk of PTS doubles (by twofold) [19].

In high-risk patients, preventing DVT with effective thromboprophylaxis and decreasing the likelihood of ipsilateral DVT recurrence are likely to lower the risk of developing PTS [5]. The American Society of Hematology (ASH) guideline panel advises lifelong antithrombotic treatment for patients with recurrent unprovoked DVT [20]. It is recommended that individuals with PTS wear 20–30 mmHg knee-length elastic compression stockings on a daily basis. Intermittent compression devices or pneumatic compression sleeve units can be explored in patients with moderate-to-severe PTS whose symptoms are not satisfactorily controlled by elastic compression stockings alone. For PTS patients who can handle it, a 6-month or longer supervised fitness training programme is appropriate[19]. A multidisciplinary approach should be used in the patient's therapy for post-thrombotic ulcers [21].

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