Letter TJH-2018-0332.R3
Accepted: 16 January 2019
Submitted: 27 September 2018

Title: Venous thromboembolism in a young girl with duplication of inferior vena cava and protein S deficiency

Authors: Wei-Li Liao, MD[1], Ming-Yang Shih[1], MD, and Jiaan-Der Wang[1,2,3], MD, Ph.D.

Affiliations:

[1]Department of Pediatrics, Taichung Veterans General Hospital, Taichung, Taiwan.
[2]Center for Rare Disease and Hemophilia, Taichung Veterans General Hospital, Taichung, Taiwan
[3]Tunghai University, Taichung, Taiwan

Running title: Venous thromboembolism in IVC Duplication

Conflict of Interest: None

Correspondence to:
Jiaan-Der Wang, MD, Ph.D.
Center for Rare Disease and Hemophilia, Taichung Veterans General Hospital, Taichung, Taiwan 40705
Tel: 886-4-23592525 ext. 5995
Fax: 886-4-2374-1359
E-mail: wangjiaander@gmail.com

To the Editor,□A previously healthy 13-year-old girl presented with a 3-day history of progressive swelling and pain at her left lower limb. She also complained of cough in the last two weeks. No trauma, surgery, travel or medication was noticed before this illness. Physical examination revealed significant swelling and tenderness at her left lower limb. The laboratory data showed a high level of D-Dimer (13.0 mg/l FEU, reference range < 0.55 mg/l FEU). The multi-detector computed tomography (MDCT) showed extensive emboli formation from left calf region to left ilio-femoral veins and duplication of inferior vena cava (IVC) (Figure 1). Pulmonary ventilation-perfusion (V/Q) scintigraphy revealed several mismatched areas diagnostic for bilateral acute pulmonary embolism. Tracing the family history, her father developed venous thromboembolism (VTE) at the age of 40 years, and was diagnosed as protein S deficiency. A thrombophilia screening in this patient identified severe protein S deficiency (protein S activity: 2%, reference range 55~140 %). Other results, including levels of homocysteine, antithrombin III, and protein C activity were within normal limits; Factor II G20210, Factor V Leiden G1691A, anti-cardiolipin antibody, and anti-β2-glycoprotein I IgM and IgG were all negative. Her symptoms and signs subsided after treatment with heparin, followed by warfarin for 3 months. The repeated measure of protein S activity was 7% after discontinuation of treatment with

warfarin for one week. Given the two provoking risk factors were present, the patient continued to receive prophylactic therapy with warfarin.

Virchow's triad describes the three main factors contributing to thrombosis, which include hypercoagulability, vessel injury and venous stasis. Congenital anomalies of IVC may predispose to VTE due to resultant venous stasis. Duplication of IVC is usually considered as asymptomatic and an incidental finding while performing retroperitoneal surgery or venous interventional radiology. However, an increasing number of studies suggested that patients with unprovoked VTE were associated with duplication of IVC [1-4]. The age of these patients ranged from 18 to 84 years. No pediatric patient was reported.

VTE is long considered to be far less common in children than in adults. Most of pediatric VTE are provoked and occur with multiple risk factors [5]. Genetic risk factors play an important role in children who develop VTE. And, a thrombophilia screening is suggested in selected patients with VTE, such as young patients. [6] Protein S deficiency leads to loss control of thrombin generation and fibrinolysis, and is associated with 5.8-fold increased odds of index VTE [7]. VTE in unusual sites has unique and obscure provoking factors [8]. Therefore, protein S deficiency was an important risk factor for the VTE event in this patient. In summary, we hypothesize that duplication of IVC and protein S deficiency both promoted intravenous thrombus

formation and predisposed the patient to develop VTE at a younger age. The combination of a rare congenital thrombophilic trait with a rare anatomic variant is very infrequent. In young age patients with VTE less common causes of thrombosis such as inherited thrombophilias and anatomic abnormalities should be considered.

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Figure 1. Left panel, contrast-enhanced CT image demonstrating duplicated inferior vena cava (whitish arrow). Right panel, from top to bottom, the arrow indicates thrombosis found in engorged left iliac vein, femoral vein and popliteal vein.

254x190mm (72 x 72 DPI)