An Uncommon Case of Lower Limb Deep Vein Thrombosis with Multiple Etiological Causes

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Conflict of interest: None declared

Patient: Female, 43
Final Diagnosis: Deep vein thrombosis
Symptoms: 2-week pain and swelling in the right leg
Medication: Enoxaparin • Warfarin
Clinical Procedure: None
Specialty: Hematology

Objective: Rare disease
Background: Deep vein thrombosis (DVT) is a type of venous thromboembolism with diverse clinical and environmental risk factors. Very few cases of DVT with multiple high risk factors have been reported. Here, we report an uncommon DVT case with multiple etiological causes, including appendicitis/appendectomy, morbid obesity, immobilization, positive phosphatidylserine IgG, and heterozygous factor V Leiden mutation.

Case Report: A 43-year-old female was brought to the emergency room because of 2-week history of pain and swelling and ultrasound revealing evidence of DVT in the right leg. One month ago, she underwent an exploratory laparotomy because of subacute appendicitis. After surgery, the patient stayed at home in bed with very limited activity. She did not have a cough, hemoptysis, chest pain, or shortness of breath. She was morbidly obese, and had a past medical history of diabetes, hypertension, and hyperlipidemia. A full coagulation workup was completed, including Protein C, Protein S, and antiphospholipid antibody, as well as factor V and prothrombin gene mutation screen. Her D-dimer was positive. Computed tomography (CT) angiography of the lungs ruled out major emboli but was unable to rule out minor emboli. A heterozygous factor V Leiden R506Q mutation was detected. Of interest was a significantly positive phosphatidylserine IgG with a value of over 42. She was started with enoxaparin (120 mg, twice a day), and warfarin was added on day 2 when pulmonary embolism was ruled out by CT angiography. The International Normalized Ratio (INR) was monitored daily to adjust warfarin dose.

Conclusions: Multiple etiological factors present in this patient may have contributed to her lower-limb DVT, including appendicitis/appendectomy, morbid obesity, immobilization, positive phosphatidylserine IgG, and factor V Leiden mutation. Therefore, it is important to follow the complete workup for hypercoagulable states. This can help with diagnosis and therapy, and also give insight into the pathogenicity, which can help with prevention of recurrence and severe complications of DVT.

MeSH Keywords: Factor V • Immobilization • Obesity • Phosphatidylserines • Venous Thrombosis

Full-text PDF: http://www.amjcaserep.com/abstract/index/idArt/902391
Background

Deep vein (or venous) thrombosis (DVT) is the formation of a blood clot or thrombus within a deep vein, predominantly in the legs [1]. Detachment of a clot that travels to the lungs may cause pulmonary embolism, a potentially life-threatening complication [2]. Collectively, DVT and pulmonary embolism constitute a single disease process termed venous thromboembolism (VTE) [2]. A diverse array of clinical and environmental risk factors contributes to venous thrombosis. The interplay of 3 processes resulting in venous thrombosis are known as Virchow’s triad: 1) venous stasis or immobilization – e.g., caused by hospitalization for acute medical illness, nursing-home residence, long-haul travel, and paresis or paralysis; 2) hypercoagulability – e.g., caused by older age, active cancer, obesity, hormonal therapy, pregnancy, positive antiphospholipid, and personal or family VTE history; and 3) vascular damage – e.g., caused by surgery, trauma and central venous catheter or pacemaker [3,4]. Genetic factors that increase the risk of VTE include deficiencies of protein C, protein S, and anti-thrombin, in addition to non-O blood type and mutations in the factor V and prothrombin genes [5–7]. Obviously, various risk factors contribute to the formation of VTE. However, very few cases of DVT with multiple high risk factors have been reported. Here, we report an uncommon DVT case with multiple causes, including appendicitis, morbid obesity, immobilization, positive phosphatidylserine IgG, and heterozygous factor V Leiden mutation.

Case Report

Chief complaint

A 43-year-old female was brought to the emergency room because of a 2-week history of pain and swelling, as well as the evidence of DVT at the right leg revealed by ultrasound. She denied having chest pain, palpitations, syncope, or difficulty breathing.

History of past illnesses

This patient was admitted to hospital for abdominal pain 1 month ago. She was diagnosed with small bowel obstruction and subacute appendicitis, and underwent exploratory laparotomy with extensive lysis of adhesions, appendectomy, and peritoneal lavage with bilateral drains placement. After surgery, the patient stayed at home in bed with very limited activity. She reported that since hospitalization, she noticed swelling of both legs. Eventually, the swelling of left leg subsided but she continued to have swelling on the right side and started having pain. Her right leg felt warm and tender when touched.

She denied any chest pain, hemoptysis, or shortness of breath (SOB). She had some cough with greenish sputum and runny nose for 3 days but no fever. She denied any hormone replacement therapy or smoking. There was no significant family medical history, particularly no clots or cancer. Of note, she was morbidly obese, and had a past medical history of diabetes, hypertension, and hyperlipidemia. Her home medications included simvastatin 20 mg daily, insulin isophane and insulin regular 55 units twice a day, metformin 500 mg twice a day, and lisinopril 20 mg daily.

Physical examination

The HEENT examinations, including head, ears, eyes, nose, and throat, showed she was normocephalic and atraumatic. The PERRLA test, including pupils equal, round, reactive to light and accommodation, was normal. The NECK examination result was normal, showing supple, non-engorged veins, and no thyromegaly. Bilateral lungs and heart examination results were normal. The abdominal examinations showed 1 incisional scar with some areas of non-healing wound with serous drainage. The neurological examination result was normal. Distal pulses on both lower extremities were palpable. In comparison with her left, her right lower extremity was swollen and had slightly high temperature. Homan’s sign and Moses sign were positive on her right leg. Her left lower extremity examination result was normal.

Her vital signs on admission showed normal body temperature (98°F [36.6°C]), slightly high blood pressure (BP) at 142/70 mmHg, normal heart rate (HR) at 90/min, normal respiratory rate (RR) at 21/min, and significantly high body mass index (BMI) at 47.3 kg/m².

Imagological examination

Electrocardiography showed a normal sinus rhythm. Duplex ultrasound of the lower extremities revealed the left popliteal vein was not fully compressible, suggesting a blood clot there. Chest x-ray did not find any infiltrates or perihilar interstitial process compared with a previous examination of July 1, 2016. Computed tomography (CT) angiography of the lungs displayed that: i) the central pulmonary arteries were normal in caliber without evidence of central thrombus, ii) no convincing filling defects were demonstrated in the more distal segmental and sub-segmental pulmonary arteries bilaterally, iii) sub-centimeter central mediastinal lymph nodes were present, and iv) mildly enlarged and hyperplastic bilateral axillary lymph nodes were present, measuring up to 1.4 cm on the right and 1.1 cm in short axis on the left. These CT findings ruled out major emboli but did not rule out minor emboli.

Laboratory examination

General hematologic analysis reported normal white blood cell count of 8.3×10^9/μL, including monocytes 0.7×10^9/μL (8.4%), eosinophils 0.27×10^9/μL (3.8%), neutrophils 5.1×10^9/μL (61%),
basophils 0.02×10^9/µL (0.2%), and lymphocytes 2.2×10^9/µL (26.7%). She had normal red blood cell count 3.86×10^12/µL, normal platelet count 259×10^9/µL, normal mean platelet volume (MPV) 10.2 fl, lower hemoglobin 9.8 g/dL, normal mean corpuscular hemoglobin concentration (MCHC) 31.5 g/dL, slightly lower hematocrit 31.1%, normal mean corpuscular volume (MCV) 80.6 fl, and normal mean corpuscular hemoglobin (MCH) 25.4 pg.

Her general chemistry and urinalysis results were normal.

Based on her manifestations and ultrasound results, thrombosis of the left popliteal and femoral veins was suspected. We completed a full coagulation workup, including protein C, protein S, and antiphospholipid antibody, as well as factor V and prothrombin gene mutation screen. General coagulation test showed normal prothrombin time (PT: 12.10 s), normal activated partial thromboplastin time (APTT: 27.2 s), lower warfarin International Normalized Ratio (INR) 1.18 (normal range 2–3), and positive D-dimer titration. Her protein C and protein S antibodies were negative. Of note, a heterozygous factor V Leiden R506Q mutation was detected in this patient. Her phosphatidylserine antibodies (IgG) were significantly positive, with a value of 42. Phosphatidylserine antibodies IgA and IgM were normal (IgA: <20; IgM: <25). Cardiolipin antibodies were normal (IgG: <14; IgA: <11; IgM: <12). B2-glycoprotein antibodies were normal (IgG: <9; IgA: <9; IgM: <9).

Treatment plan

The patient was started with enoxaparin (120 mg, twice a day), and warfarin (starting from 7 mg daily) was added on day 2 when pulmonary embolism was ruled out by CT angiography. The International Normalized Ratio (INR) was monitored daily to adjust warfarin dose until INR is stabilized at between 2 and 3.

Discussion

In recent years, there have been more diagnoses of DVT than any other medical illness because of population aging, increased surveillance, improved diagnostic ability, and a higher prevalence of comorbidities such as obesity, cancer, chemotherapy, and surgery [8–10].

In the past, it was considered that if there had been immobilization and an added risk factor such as the above-mentioned conditions, it was sufficient to make the diagnosis and start anticoagulation [11]. Commonly, the treatment was given anywhere from 3 months to 6 months [12]. However, it has become more complex since identifying conditions promoting hypercoagulability, such as factor V Leiden and prothrombin gene mutations, homocysteinemia, antiphospholipid syndrome, and congenital deficiency of factor S, factor C and anti-thrombin 3, as well as some of rare conditions such as plasminogen inhibitors. If these situations are present in a recessive fashion, a second risk factor is necessary to promote thrombogenesis.

Our patient had multiple risk factors, including appendectomy, morbid obesity, immobilization, positive phosphatidylserine IgG, and heterozygous factor V Leiden mutation. To prevent further propagation of the clot, she needed to be observed closely and may need further tests to rule out conditions such as atypical lupus.

In addition, D-dimer was positive in this patient. D-dimers are a fibrin degradation product, and an elevated level can result from plasmin dissolving a thrombus or it may be due to other conditions such as an indwelling catheter [13]. An elevated level requires further investigation with diagnostic imaging to confirm or exclude the diagnosis. When individuals are at a high risk of having DVT, diagnostic imaging is preferred to a D-dimer test [13], while for those with a low or moderate probability of DVT, a normal D-dimer level may exclude a diagnosis [13]. Of note, this patient had positive phosphatidylserine IgG, which could be additional risk for DVT. Patients with positive phosphatidylserine IgG may need at least 6-month anticoagulation therapy and a close follow-up in clinic to periodically reassess recurrent DVT risks, especially anti-phosphatidylserine antibody, to ascertain that extended treatment is appropriate [14,15]. Furthermore, mutation of factor V Leiden, which makes factor V resistant to inactivation by activated protein C, moderately increases risk for VTE by 3 to 8 times [16,17], whereas mutations of factor S, factor C, and anti-thrombin 3, which normally prevent blood from clotting, increase the risk of VTE by about 10 times [17], and the genetic variant prothrombin G20210A, which causes increased prothrombin levels, increases risk of VTE by 2 to 3 times [18]. Recently, it was reported that following extensive surgery, a trauma case developed multiple venous thrombosis and then life-threatening bleeding caused by acquired hemophilia, which was complicated by factor VIII deficiency [19]. Although heritable risk factors only slightly predict recurrent DVT and have limited relevance for the long-term management of DVT, thrombophilia testing is still necessary since it can provide useful information for genetic consulting.

Conclusions

We now live in an era in which we may have to perform the entire hypercoagulable workup, even in a straightforward case of DVT. This helps with diagnosis and therapy, and also gives insight into the pathogenicity.
In the future, we will be more confident in treating patients in more efficient ways and also in knowing whether patients need temporary or indefinite therapy once all the information is available, which could help prevent the recurrence and severe complications of DVT.

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Conflict of interest

The authors declare no conflict of interest.