Pulmonary Emboli and Deep Venous Thrombosis during Adolescence

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ABSTRACT

Pulmonary emboli (PE) and deep venous thrombus (DVT) are two conditions considered to affect primarily adults. These conditions, however, can and do affect neonates, toddlers, school-age children, and adolescents. Factors contributing to the development of PE and DVT are often associated with genetic mutations in Antithrombin III, Protein C, and Protein S. This article presents a primary care case study of an adolescent who was diagnosed with and underwent treatment for bilateral PE and a DVT, and reviews the underlying primary genetic mutations, diagnostic workup, and management of his clinical condition. J Pediatr Health Care. (2017) ■■, ■■-■■.

KEY WORDS

Clotting disorder, PE, thrombophilia, venous thrombosis

The occurrence of pulmonary emboli (PE) and deep venous thrombosis (DVT) is uncommon in children. Children who are at greatest risk for DVT are neonates, followed by adolescents, toddlers, and school-age children (Bruwer et al., 2016). Symptoms of DVT in children include swelling in an upper extremity or calf pain (Hennelly et al., 2016). This article presents a case encountered in a pediatric primary care setting and discusses the underlying pathophysiology, diagnostic workup, and management of the patient's condition.

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CASE REPORT

A well-developed, 17-year-old White male presented to the pediatric primary care office complaining that his cough was not improving and that his symptoms were worse. The adolescent had been seen 3 days prior at an urgent care center for cough and fever. He was diagnosed with pneumonia and prescribed azithromycin.

Review of the adolescent's health history during the office visit showed that his family and medical histories were negative for any major illness and that he had not had any surgical procedures. The review also showed that he was last seen in the office 3 years earlier for a physical examination. He was considered healthy at that time.

Review of the adolescent's current history showed that he had just completed the regimen of Zithromax and that he was not taking any other medications. He reported that there was no history of injury or recent prolonged travel. He also disclosed that he was a member of his school's rowing team.

The adolescent's vital signs were as follows: temperature = 37.2 °C, pulse = 86 beats per minute, respirations = 24 breaths per minute, and blood pressure = 128/76 mm Hg. While conducting the physical examination, the pediatric nurse practitioner (PNP) asked the adolescent to take a deep breath. He responded, "I can't." The PNP asked him to try again and found that he, in fact, was physically unable take a deep breath. During the examination, the adolescent also told the PNP that his left leg hurt. Upon examining his left leg, the PNP found that his skin was warm, dry, and pink; cutaneous signs of discoloration, ecchymosis, induration, or visible venous distention were not present; and popliteal and dorsalis pedis pulses were present. His left calf measured 5 cm larger in circumference than his right calf, and he had a positive Homan's sign.

The adolescent was sent to the emergency department for further evaluation and treatment. Diagnostic evaluation included a prothrombin time (PT), partial thromboplastin time (aPTT), platelet count, thrombin time, fibrinogen level, fibrin degradation products level, D-dimer testing, ventilation/perfusion scan, and ultrasonography of his left leg. Results from the laboratory work were as follows (values appearing in parentheses are normative value ranges for healthy individuals): PT = 13 seconds (10–15 seconds), aPTT = 38 seconds (20-40 seconds), thrombin time = 10 seconds (3 seconds < control value), and fibrinogen = g/L 3.25 (2-4 g/L). His fibrin degradation products level was greater than 10 µg/ml (< 10 µg/ml), and the D-dimer test result was positive, with a value greater than 0.4 µg/ml. Results from the ventilation/perfusion scan and ultrasonography found that the adolescent had bilateral pulmonary emboli and a DVT extending from his left knee to his ankle.

The adolescent was subsequently hospitalized and was treated with heparin for 10 days. His aPPT was maintained at 1.5 to 2.5 times the upper limit of normal (Konstantinides, Barco, Lankeit, & Meyer, 2016; Raffini & Scott, 2016b). Surgical intervention to remove the thrombosis was not considered. Ultrasonography of his left lower leg was repeated on Day 8 of treatment and showed that the thrombosis had resolved.

Additional laboratory work was conducted during the adolescent's hospital stay to determine possible factors that contributed to the development of his PE and DVT. Tests for underlying factors included a liver panel; peripheral blood smear; levels of immunoglobulin G, immunoglobulin M, antiphospholipid antibodies, anticardiolipin antibodies, and lupus anticoagulant; DNA analysis for Factor V Leiden; homocysteine levels; Factor VIII; C-reactive protein level; and functional assays for antithrombin III deficiency (ATD), protein C deficiency (PCD), and protein S deficiency (PSD). Results from this workup showed that the adolescent had ATD. His diagnosis at discharge was spontaneous, idiopathic thromboembolic event due to ATD. The adolescent was discharged to home taking warfarin. He was scheduled for follow-up visits with a hematologist in 1 week and with his primary care provider in 2 weeks.

DISCUSSION

Development of PE and DVT is often attributed to conditions classified as primary or secondary. Primary causes, which are linked to genetic mutations, include ATD, PCD, and PSD. Other mutations, such as Factor V Leiden and methylenetetrahydrofolate reductase (*MTHFR4*), are not considered primary causes. Secondary causes contributing to the development of PE and DVT include oral contraceptive use (estrogen), recent immobilization, previous history of DVT/PE, liver disease, nephrotic syndrome, disseminated intravascular coagulation, and trauma (Hennelly et al., 2016).

The role of antithrombin III is to inhibit thrombin and Factors IX, X, XI, and XII (Desai, 2007). In addition, antithrombin III formation is not dependent on vitamin K (Raffini & Scott, 2016a). Deficiencies in antithrombin are classified as Type I, a deficiency in the antigen and functional activity, or Type II, a dysfunctional form in which the functional activity of the antigen is reduced. Males and females of all races presenting with a DVT or PE due to ATD are usually in their mid to late teens and have heterozygous mutations. Infants born with homozygous mutations typically present with neonatal purpura fulminans and seldom survive (Limperger et al., 2014; Raffini & Scott, 2016a). Thrombosis resulting from ATD usually occurs in the iliofemoral veins of the lower extremity or mesenteric veins, vena cava, renal veins, or retinal veins. Drugs used in the treatment of ATD include heparin and warfarin (Schwartz, McCance, & Rote, 2017). A synthetic androgen, danocrine, can also be used to increase antithrombin levels but has not been approved for use in children. Two other medications, ATnativ (Kabi Vitrum, Stockholm, Sweden) and Thrombate III (Miles, Cutter Biological, West Haven, CT), which are synthetic antithrombin concentrates, are also available for use in the treatment of ATD (Gruppo, Leimer, Francis, Marlar, & Silberstein, 1988; Raffini & Scott, 2016b; Wong et al., 2013).

Protein C inhibits coagulation and is activated when it binds to the thrombomodulin-thrombin complex. Protein C, however, is dependent on vitamin K for its development (Schwartz et al., 2017). After being activated, Protein C inhibits the activation of Factors V and VIII. Thus, deficiencies in Protein C can lead to the development of a DVT (Desai, 2007). Deficiencies in Protein C are classified as Type I, a reduction in the number and functional activity of the antigen, and Type II, a reduction in the functional activity of the antigen. Thrombolytic events associated with PCD usually occur spontaneously in the late teens to early twenties (Schwartz et al., 2017). Deficiencies in Protein C can also be treated with Danazol. Danazol increases Protein C in 10 to 20 days; however, its efficacy has not been established in children (Raffini & Scott, 2016b; Wong et al., 2013).

Protein S also inhibits coagulation and is dependent on vitamin K for its formation. Protein S acts as a cofactor to Protein C and enhances its action (Klostermeier et al., 2015; Raffini & Scott, 2016a; Schwartz et al., 2017). Like ATD and PCD, Protein S deficiencies are classified as Type I and Type II. Type I has quantitatively fewer numbers of antigens and reduced functional activity of the antigen (Raffini & Scott, 2016a); Type II results in reduced functional activity of the antigen (Schwartz et al., 2017). Infants born with homozygous mutations may develop neonatal purpura