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Unilateral calf pain in the pediatric emergency department

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Abstract

Unilateral calf swelling and pain is not a common complaint in the pediatric emergency department. We present a case of a 17-year-old male with no past medical history who presented with left leg swelling and pain while taking prednisone and isotretinoin. He was found to have an extensive occlusive thrombus throughout the deep venous system in his left leg. He was later diagnosed with May-Thurner syndrome, an anatomic variant in which the right iliac artery compresses the left iliac vein. We review the differential diagnosis, diagnostic work-up and initial ED management of deep venous thrombosis and provide a brief discussion of May-Thurner syndrome and the association of isotretinoin and vascular thrombi.

The diagnosis of deep venous thromboembolism (DVT), while common in the adult emergency department (ED) population is infrequent in the pediatric ED. We present a case of an extensive DVT in a 17-year-old male who presented with unilateral leg pain and swelling, and was later diagnosed with May-Thurner syndrome. We review the differential diagnosis, diagnostic testing, and initial management of suspected DVT in the emergency department.

Case

A 17-year-old male, with no significant past medical history, presented to the ED of a tertiary children's hospital with one week of left leg swelling and pain. Two weeks prior, he was treated with cephalexin and a prednisone taper for contact dermatitis on both lower extremities. He discontinued the prednisone taper five days prior to presentation, due to the onset of increasing left-sided calf pain and swelling, thought to be worsening contact dermatitis. Erythema, pain and swelling had spread up to his left groin area and he developed difficulty walking. The pain was not relieved by over-the-counter analgesics. He had no allergies and his only other medication was isotretinoin, which finished on the day of presentation, after a six month course. There was no history of surgery, central venous lines or in-dwelling catheters. A review of systems was negative for chest pain, shortness of breath, cough, fever, malaise, visual changes, headache, weakness, or pain and swelling in other areas of the body. The patient denied recent travel, immobilization, smoking and drug use. There was no family history of cancers, blood clots, cardiac problems, early death or use of blood thinners.

Initial vital signs were temperature 37.7C, heart rate 92, respiratory rate 20, and blood pressure 131/66 and oxygen saturation 100%. The patient reported 6/10 pain in his left leg. There was marked edema starting at the groin and moving distally. The left calf was tense

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and tender to deep palpation and 5cm greater in circumference than the right calf. There was diffuse tenderness in the groin without lymphadenopathy. Leg pain was exacerbated by walking and passive dorsiflexion of the left foot (Homans' sign). Cardiac exam showed regular rate and rhythm without murmurs, rubs or gallops. Breath sounds were clear and equal bilaterally, with no increased work of breathing or chest tenderness. The abdomen was soft, non-tender, with normal bowel sounds. Head, neck, and upper extremity exams were unremarkable.

Due to concern for DVT, a Color Doppler ultrasound was performed. It showed extensive occlusive thrombus with no flow, extending from the left popliteal vein through the left femoral vein and into the left external iliac vein. There was also non-occlusive thrombus within the left greater saphenous and left profunda femoris veins. There was no thrombus in the right leg.

Laboratory studies were notable for an elevated white blood cell count of 13.7, D-dimer of 4.04ug/mL [normal < 1.30] and elevated fibrinogen of 586mg/dL [normal 150–350 mg/cL]. Coagulation studies, creatinine kinase and electrolytes were within normal limits. A hypercoagulability panel was drawn.

The decision was made to defer mechanical intervention and treat the patient with enoxaparin subcutaneously. Vital signs remained stable and the patient was admitted for anticoagulation and further evaluation and management.

On day two of admission, a venogram showed the superior extension of the thrombus to be located above the bifurcation of the inferior vena cava. Initial attempts at mechanical clot removal by interventional radiology were unsuccessful, and catheters were placed for continuous tissue plasminogen activator (t-PA) and heparin infusions. After three days of t-PA infusions, an abdominal CT scan showed persistent clot in the left common iliac to the left femoral vein, but no evidence of external compression by lymphadenopathy or external clot. A repeat venogram, however, showed evidence of compression of the left common iliac vein by the right common iliac artery (May-Thurner syndrome, see below). Some clot remained in the common iliac vein.

The left common iliac vein and external iliac vein were both stented, and the t-PA infusion was stopped. The patient continued on systematic anticoagulation with IV heparin. Extensive hypercoagulation workup, including protein C, protein S, antithrombin III and homocysteine levels and tests of Factor V Leiden, prothrombin, and methylenetetrahydrofolate reductase (MTHFR) were all normal. During the hospital stay, the patient developed chest pain and was found to have a small right pulmonary embolus (PE). Anticoagulation was transitioned from heparin to oral warfarin, and the patient was discharged home on crutches in stable condition with an INR of 2.85.

Six days after discharge, the patient presented to the pediatric ED with increased pain and swelling of his left leg, which started as soon as he began walking without his crutches. Doppler ultrasound showed the recurrence of occlusive thrombus throughout the left deep venous system, despite an INR >4.0. He was again admitted for t-PA and heparin infusions. Having failed anticoagulation therapy, he had an IVC filter placed to prevent pulmonary embolism. This second admission was complicated by progressive thrombocytopenia during the heparin infusion. Heparin-mediated platelet antibody testing by ELISA was positive, supporting a diagnosis of heparin-induced thrombocytopenia. Anticoagulation was transitioned from heparin to argatroban before being transitioned to oral warfarin. He was again discharged in stable condition.

Discussion

Venous thromboembolism (VTE), consisting of both DVT and PE, is an underrecognized cause of morbidity and mortality in pediatric patients. Compared to the high incidence of VTE in older adults (0.5% per year in those age 80), VTE is relatively rare in childhood [1]. In the United States, data from the National Hospital Discharge Survey showed an incidence of VTE in childhood of 0.49 per 10,000 per year [2]. In the pediatric population, there is a bimodal distribution of VTE, with peaks in the neonatal period and in adolescence. Among 15–17 year-old adolescents, the incidence is 1.1 per 10,000 [2,3].

The contributors to DVT are classically grouped as Virchow's triad: venous stasis, endothelial damage, and hypercoagulable state. In the pediatric population, the single greatest risk factor for DVT is the presence of an in-dwelling central venous catheter, leading to endothelial damage [4]. Over 50% of DVTs in children and over 80% in newborns occur in conjunction with such catheters [3,5,6]. The underlying conditions associated with central venous catheter placement, including malignancies, hematologic disorders treated with bone marrow transplantation, congenital heart disease and infectious diseases may also contribute to the development of DVTs. Venous stasis can result from casting or splinting, post-operatively, or after prolonged immobility. Children may also have inherited or acquired pro-thrombotic conditions, including anticoagulant deficiencies, Factor V Leiden or prothrombin gene mutations, disseminated intravascular coagulation, and increases in factor VIII activity with infection or inflammation. In females, estrogen-containing oral contraceptive pills (or pregnancy) increase the risk of DVT, especially among those with an underlying Factor V Leiden mutation [3].

The diagnosis of VTE requires a high degree of clinical suspicion. Important elements of the history include presence or history of a central venous catheter, personal or family history of clots or prothrombotic state, other past medical history, and history of immobilization. The classic presentation of an extremity DVT is unilateral pain and swelling of the involved limb. Upper extremity DVT may extend into the superior vena cava and cause neck and face swelling, periorbital edema, or headache. Patients may also present with symptoms of PE: shortness of breath, tachypnea, pleuritic chest pain or hypoxemia. Extremity symptoms usually begin gradually and progress over days, whereas PE symptoms usually have sudden onset [7].

Physical findings consistent with lower extremity DVT include unilateral swelling, warmth, or erythema. The course of the involved vessel may be tender, and occasionally the actual clot can be palpated. Superficial and collateral veins may be prominent. Homans' sign, pain in the posterior calf with passive dorsiflexion of the foot, has been shown to be unreliable in diagnosis, positive in 8–56% of patients with DVT, and greater than 50% of symptomatic patients without DVT [7,8]. Patients with major occlusion of the iliofemoral venous system may show a bluish discoloration of the leg, or, if tissue pressures exceed perfusion pressures, the leg may turn white. Either of these are a medical emergency, indicating a risk for gangrene, shock, and PE. Unfortunately, physical exam is unreliable in the diagnosis of DVT. Findings on physical exam may reinforce the clinical suspicion of DVT, but an equivocal exam cannot be used to exclude the diagnosis in a patient with a suggestive history.

Diagnosis of DVT requires radiographic imaging, usually ultrasound. The theory of venous ultrasound is that presence of a thrombus in a vein prevents the vein from compressing. Doppler ultrasound can also be used to assess flow within a vessel. Ultrasound has the highest sensitivity for diagnosing proximal DVT, but is much less reliable for calf DVT. For all DVTs, ultrasound has a sensitivity of 89%, specificity of 94%, positive predictive value

of 94%, and negative predictive value of 90% [9,10]. For proximal DVT, the results are notably better: sensitivity of 95%, specificity of 96%, positive predictive value of 97% and negative predictive value of 98%. The advantages of ultrasound include non-invasiveness, lack of exposure to radiation, relatively low cost and wide availability in the ED setting. The disadvantages include the limited utility for pelvic, upper extremity, or superior vena cava DVTs, operator dependence and technical difficulty in obese patients or patients with significant edema. Additionally, acute and chronic thrombi appear similar on ultrasound, making it difficult to differentiate recurrent and remaining thrombus.

Several additional radiographic studies can be used for the diagnosis of DVT. The gold standard diagnostic test is contrast venography, but it is invasive, expensive, and the contrast can cause allergic reactions or post-injection DVT. It does, however, allow detection of DVTs in areas where ultrasound has poor sensitivity, including the calf, inferior vena cava, and upper extremity veins. MRI is another non-invasive method of diagnosis with high sensitivity, but it is expensive and not ubiquitously available. It can, however, distinguish between acute and chronic thrombi, is safe in pregnancy, and can diagnose alternate causes of symptoms, such as pelvic masses or lymphadenopathy. Another option involves using helical CT pulmonary angiography to image the lower extremity veins, allowing a single study to assess for both DVT and PE.

Measurement of the D-dimer, a fibrin break-down product, is most useful in ruling out DVT in patients with a low pre-test probability. D-dimer levels can be elevated in a variety of disorders, including sepsis, stroke, myocardial infarction, DIC, cancer, liver disease, trauma and pregnancy [10–12]. The pre-test probability can be determined by using the Wells criteria, which gives a numeric score based on a variety of risk factors (see table)[13]. This probability can then be used to determine which other studies are necessary. Our patient had a Wells score of 3 (localized tenderness, swollen leg, pitting edema), indicating a high probability of DVT, so an ultrasound was necessary regardless of D-dimer. His markedly increased D-dimer did increase the suspicion of DVT, and it correlated with his large thrombus burden.

The differential diagnosis of a painful, swollen limb is broad, although the history of symptom onset and the physical exam can help to distinguish between the possibilities. The differential includes trauma, external compression of a vein by tumor or lymphadenopathy, compartment syndrome, cellulitis, myositis, Baker cyst, abscess and tumor. Congestive heart failure, nephrotic syndrome, liver disease, pregnancy and capillary leak syndrome usually cause bilateral symptoms, whereas DVT is usually unilateral. Sudden onset of symptoms, particularly during activity, is more characteristic of a musculoskeletal or traumatic process. Cellulitis and compartment syndrome often present with fever, chills and leukocytosis. DVT can also cause fever, although it typically is low-grade. A ruptured Baker cyst can cause symptoms indistinguishable from DVT, including a positive Homans' sign [7,8]. A Baker cyst is a popliteal cyst filled with synovial fluid behind the knee. Patients may have both a Baker's cyst and a DVT [14].

The main principles of treatment involve reestablishing flow through the affected vessels, preventing embolization and post-thrombotic syndrome and preventing recurrence. Unfortunately, there are few studies in pediatrics to guide treatment choices, and most recommendations are based on data from adults [15]. Most children are treated initially with unfractionated heparin with a goal aPTT of 60–85, and later transitioned to warfarin or low-molecular weight heparin for several months, depending on the underlying cause and thrombosis risk factors. The role of thrombolysis in pediatrics is unclear, as no randomized controlled studies exist, and published reports, usually case reports or small series, use non-standardized thrombolytic regimens, include children of different ages, children with arterial

or venous thrombi, and have variable reporting of outcomes and complications [4,16,17]. The main risks are bleeding complications, which are quite common, but in carefully selected pediatric patients, thrombolysis may decrease the risk of post-thrombotic syndrome, and should be considered [16,17]. The role of the ED physician should be mainly diagnostic, although early consultation with vascular surgeons, hematologists and radiologists will help guide the initiation of treatment, evaluation for hypercoagulability and the need for supportive diagnostic imaging.

May-Thurner syndrome is an anatomic variant in which an overriding right common iliac artery compresses the left common iliac vein. This chronic compression leads to changes in the intima of the vein, leading to the formation of venous “spurs” and stenosis of the vessel [18,19]. This stenosis predisposes patients to thrombosis and occlusion of the left deep venous system. The mean age of presentation is around 40 years of age, and there is a female predominance [20]. Several cases of adolescent females found to have May-Thurner syndrome after presenting with left-sided DVT have been reported [21,22]. Interestingly, in most of these cases, another risk factor for VTE was present (oral contraceptive use, underlying hypercoagulability).

Vascular thrombus and thromboembolic phenomena have been reported as rare but serious adverse reactions to isotretinoin. The Canadian Adverse Reaction Newsletter reported 11 cases of thrombosis, myocardial infarction, stroke and pulmonary embolism associated with isotretinoin use between 1983 and 2005 [23]. A case of central retinal vein occlusion associated with isotretinoin recently has been reported [24]. The role of isotretinoin in the development of the DVT in the patient reported here is unclear. His last dose of a six-month course was the morning of his first admission, and he had a recurrent clot after discontinuing the medication. It is possible, however, that a prothrombotic effect of isotretinoin, coupled with his congenital anatomic variant (May-Thurner syndrome) created the conditions for the development of his extensive thrombus.

Conclusion

Although rare, the diagnosis of DVT in the pediatric population is well-documented and has serious consequences if not diagnosed and treated in a timely manner. Our male adolescent did not have traditional risk factors for DVT, such as immobilization, endothelial damage or hypercoagulability, but had extensive thrombus, possibly related to isotretinoin use in the setting of May-Thurner Syndrome. Emergency physicians should consider DVT in the differential diagnosis of any patient with extremity pain and swelling.

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Table 1

From:

¹³. Wells PS, Anderson DR, Bormanis J, et al. Value of assessment of pretest probability of deep-vein thrombosis in clinical management. *Lancet*. 1997. 350: 1795-8.

Clinical Feature	Score
Active cancer (treatment ongoing or within the last six months or palliative)	1
Paralysis, paresis or recent plaster immobilization of the lower extremities	1
Recently bedridden for more than 3 days or major surgery within 4 weeks	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling by more than 3 cm when compared with the asymptomatic leg (measured 10 cm below the tibial tuberosity)	1
Pitting edema (greater in the symptomatic leg)	1
Collateral superficial veins (non-varicose)	1
Alternative diagnosis as likely or greater than that of deep-vein thrombosis	-2
Low probability 0 or less, moderate probability 1-2, high probability 3 or more	