Venous Thromboembolism: Mechanisms, Treatment, and Public Awareness

A Clinical Perspective of Venous Thromboembolism

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A large number of individuals develop venous thromboembolism (VTE) every year. Each patient’s episode of DVT or PE is, naturally, unique. To highlight a variety of aspects about VTE a compilation case is presented that is composed of clinical data and images from several real patients.

Clinical Presentation

History of Present Illness

A 36-year-old woman presents to the Emergency Department with severe shortness of breath and moderately intense anterior chest pain, worse on deep inspiration, which had started suddenly that morning. She also reports a 6-wk history of mild shortness of breath, for which she had been seen 4 wk earlier by her primary care physician who diagnosed her with “asthma.” Bronchodilators and steroids were prescribed but led to no significant improvement in her symptoms. She also gives a history of mild left calf pain that had started about 2 months earlier without preceding trauma, immobilization, or surgery. Her primary care physician had seen her and prescribed Ibuprofen for a “pulled muscle.” However, in the 1 week before her present presentation her leg symptoms worsened, and she had increased diffuse leg pain and swelling and slightly bluish discoloration of the whole leg.

Her past medical history is only significant for an appendectomy at age 16. She has never been pregnant. She is on no medications, except for an estrogen and progestin-containing oral contraceptive, started 10 months earlier. She does not smoke. There is no family history of venous thromboembolism, although the patient reports that her paternal grandmother had a “swollen leg for many years” until she died in her 70’s, but no further details are known of the patient.

Physical Examination

The patient’s weight is 86 kg and her height 165 cm, calculating to a body mass index (weight divided by [height in meters]²) of 31.6 kg/m², ie, she has grade 1 obesity. Her blood pressure is 130/85 mm Hg, she is tachycardic with a heart rate of 120 /min, and tachypneic with a respiratory rate of 32 /min. Pulse oximetry with the patient at rest and breathing room air shows a low oxygen saturation of 87%. She is in moderate respiratory distress while lying in bed, and gets more short of breath while talking and when moving, such as sitting up or turning to her side during the physical examination. The lungs are clear to auscultation, and cardiac auscultation is unrevealing. She avoids putting weight on her left leg because of pain (Figure 1). The whole left leg is slightly reddish-bluish discolored and is diffusely swollen. The left midcalf is 2.5 cm in circumference larger than the right, and the midthigh 4 cm larger than the right. She has pitting edema of the left leg. The rest of the physical examination is normal.

Working Diagnosis

The Emergency Department physician has a suspicion that the patient’s acute and subacute shortness of breath may be attributable to pulmonary embolism (PE). This is heightened because the patient has several risk factors for venous thromboembolism: (1) oral contraceptive use, (2) grade 1 obesity, (3) possible family history of DVT (paternal grandmother). Further support for the presence of PE comes from the fact that she has unilateral leg symptoms suggestive of DVT: pain, swelling, bluish discoloration of the leg, and pitting edema.

Comments

Pulmonary embolism (PE) can present with varying degrees of severity of (1) shortness of breath, (2) chest pain, particularly on deep inspiration, (3) nonproductive cough, and (4) hemoptysis. A massive PE that occludes the main pulmonary artery can lead to sudden death. Submassive and smaller PEs may lead to lesser symptoms. Small PEs are often asymptomatic. The onset of symptoms can be sudden or can occur insidiously over several weeks, months, or years. In the patient discussed here a diagnosis of new onset of asthma is unlikely in view of the absence of asthma as a younger person. PE is not infrequently missed or misdiagnosed as something else, such as bronchitis, pneumonia, musculoskeletal problem, or osteochondritis, because symptoms can be very nonspecific.

DVT of the legs can present with varying degrees of severity of (1) leg swelling, (2) leg pain, (3) warmth, and (4) bluish skin discoloration. Symptoms are typically diffuse. If symptoms of tenderness, pain, redness, and warmth in the leg occur localized, a superficial thrombophlebitis should be suspected. A palpable clot, such as a subcutaneous cordlike firmness, is also indicative of a superficial thrombophlebitis, not a DVT. The onset of symptoms of DVT can be sudden or occur slowly over days to weeks. DVT is not infrequently missed or mis-diagnosed as something else, such as “Charley
A score of 5 or more out of 12, or presence of clinical symptoms and signs of DVT, heart rate >100/min, absence of other underlying disease, making PE the most likely diagnosis. A D-dimer test would not be helpful. The patient should undergo a lung imaging study to evaluate for PE. A PE-protocol CT scan shows massive pulmonary embolism in the right and left main pulmonary arteries (Figure 2). A venous compression Doppler ultrasound (synonym: Duplex ultrasound) of the left leg shows that the common femoral and femoral veins are noncompressible and blood flow is absent (Figure 3), consistent with proximal left leg acute to subacute DVT. There is no evidence of DVT in the right leg. An echocardiogram is obtained to further assess the severity of the PE and evaluate for possible right ventricular strain. It demonstrates moderately elevated pulmonary artery pressures and a moderately dilated right ventricle and atrium. The PE is classified as "submassive PE with right ventricular strain."

**Comments**

**Diagnosis of PE**

To diagnose PE, several imaging modalities exist: (1) ventilation-perfusion (VQ) nuclear medicine scan, (2) PE-protocol CT angiography (synonyms: spiral CT; helical CT), (3) chest MRA, and (4) conventional intravenous contrast pulmonary angiogram. The VQ scan is a well validated imaging study to rule out PE. However, PE-protocol chest
CTs (Figure 2) are increasingly replacing VQ scans as the diagnostic method of choice, as they are easier and faster to perform and have good performance characteristics.\(^6\) Their predictive value with a concordant clinical assessment is high, but additional testing is necessary when the clinical probability is inconsistent with the imaging results.\(^7\) Conventional intravenous (i.v.) contrast pulmonary angiogram, once considered to be the gold standard for the diagnosis of PE, is rarely done nowadays, as the test is invasive and not widely available.

**Diagnosis of DVT**

Venous Doppler ultrasound is the most widely used imaging study to look for DVT of the legs (Figure 3). Sensitivity and specificity of the test are operator-dependent. An experienced ultrasound technician or physician are, therefore, key in obtaining reliable results. Conventional ascending contrast venography of the legs is, by some investigators, still considered the gold standard for the diagnosis of PE. However, it is invasive and technically difficult and is, therefore, not typically performed as the routine test when assessing for DVT. CT venography gives good results and is a sensitive test for proximal DVT. However, it is expensive, associated with radiation exposure, not widely available, and is, therefore, usually not performed as the routine test for the diagnosis of DVT. Magnetic Resonance Venogram (MRV) of leg or pelvic veins (Figure 4) is a sensitive test to detect leg DVTs. However, it is not widely available.

**Acute Therapy**

**Inpatient Versus Outpatient Treatment**

In several well conducted studies outpatient management of patients with VTE (DVT and PE alike) has been shown to be safe, feasible, and cost-effective.\(^8,9\) However, the patient presented here is too sick to be managed at home—she has significant shortness of breath with hypoxia at rest. Her treating physician wants to give her supplemental oxygen and keep her under close observation. She needs good pain control. She is admitted to an intensive or intermediate care unit bed.

**Immediate Anticoagulant Therapy**

A patient with acute VTE needs to be anticoagulated to prevent extension of thrombus and decrease mortality. Intra-
venously low molecular weight heparin (LMWH) and Fondaparinux are all effective and acceptable treatment options for acute DVT and PE. In the patient presented here, who is potentially unstable, unfractionated heparin is preferable, because it has a short half-life and can easily be dose-adjusted, discontinued, or reversed (with protamine) in case bleeding occurs or thrombolytic therapy is considered.

Oral vitamin K antagonists (coumarins, like warfarin, phenprocoumon, or acenocoumarol; indandiones) can be started on day 1 of presentation. However, they should not be started without concomitant use of a parenteral anticoagulant in patients with acute VTE, because lowering of the natural anticoagulant protein C (half life: 9 h) on initiation of vitamin K antagonists leads to a hypercoagulable state before lowering of prothrombin (half life: 60 h) leads to protective anticoagulation. This may lead to progression of thrombosis and, on rare occasion, to warfarin skin necrosis. In the patient presented here, i.v. unfractionated heparin is started and activated partial thromboplastin time (aPTT) monitored. Vitamin K antagonist therapy is not yet started, because the treating physicians are considering giving thrombolytic therapy.

**Thrombolytic Therapy**

In a prospective randomized trial in patients with submassive PE, thrombolytic therapy did not decrease mortality compared to no thrombolytic therapy. It is not known whether thrombolytic therapy decreases the risk of long-term complications of pulmonary hypertension or the postthrombotic syndrome by opening the pulmonary arteries or deep veins of the legs faster than the patient’s own natural fibrinolytic system. Although thrombolytic therapy does carry a risk of severe bleeding, in carefully selected patients it has been shown to be relatively safe and not lead to more serious bleeding events than treatment with unfractionated heparin alone.

In the patient presented here, the treating physicians are aware of the lack of benefit of thrombolytics on mortality and the absence of data examining the long-term effect of thrombolytic therapy on risk of pulmonary hypertension and postthrombotic syndrome. However, because the physicians believe there may be a benefit on these long-term complications and because the patient has a low risk for bleeding, thrombolytic therapy is chosen after full discussion with the patient. Tissue plasminogen activator (tPA) is given: (10 mg bolus i.v., followed by 90 mg i.v. over the next 2 h).

Twenty-four h later the patient reports less shortness of breath. Her respiratory rate at rest is now 20/min, her pulse oximetry shows 92% saturation at room air. Follow-up chest CT scan shows moderate improvement in PE but significant residual thrombus in several lobar pulmonary arteries. Her leg feels a little better, even though objective circumference measurements show no improvement. However, a follow-up Doppler ultrasound of the leg veins shows partial resolution of the thrombus in the common femoral and femoral vein. Overall, it is concluded that there has been mild to moderate symptomatic improvement. Unfractionated heparin is continued. The patient’s blood platelet count is closely followed, as heparin-associated thrombocytopenia (HIT) can occur on heparin. HIT always needs to be considered in a patient on heparin (unfractionated heparin or low molecular weight heparin) who develops a new thrombotic event or has a platelet count decrease of >30% from baseline or below 100 000×10⁹/mL. It is a potentially devastating complication of unfractionated heparin, less commonly of low molecular weight heparin therapy. Venous and arterial thromboembolic complications can occur, as well as skin necrosis.

**Patient Education**

While in the hospital, the patient receives patient-friendly education material on DVT, PE, warfarin, vitamin K and diet, the factor V Leiden mutation, and the postthrombotic syndrome, which the physicians print from the website www.nattinfo.org. The patient is also made aware of the education website www.fvleiden.org. She is discharged home on warfarin, with a target International Normalized Ratio (INR) of 2.0 to 3.0.

**Thrombophilia Work-Up**

**Case Continuation**

On presentation to the hospital and confirmation of a diagnosis of DVT and PE, and before initiation of warfarin therapy, laboratory work up is done to look for an underlying thrombophilia. Nothing in the history and physical examination suggests malignancy. The laboratory testing prior to thrombolytic and vitamin K antagonist anticoagulation therapy, but while the patient is receiving heparin, shows (1) heterozygous factor V Leiden, (2) low protein S activity (patient: 46%; normal range: 62 to 140%), (3) decreased antithrombin activity (patient: 54%; normal range: 66 to 128%). She has normal values for protein C activity and serum homocysteine, the prothrombin 20210 mutation is not present, and antiphospholipid antibody testing (lupus anticoagulant, anticardiolipin antibodies, and anti-β₂-glycoprotein-I antibodies) is negative.

**Comments**

Opinions vary as to what constitutes an appropriate thrombophilia workup and who should be tested. If testing is done, then appropriate timing of testing and correct interpretation of test results is essential, as well as education of the patient about the detected thrombophilia, and of the patient’s family in the case of an inherited disorder. Acute thrombosis, heparin and vitamin K antagonist therapy, as well as hormonal therapy, pregnancy, and inflammatory disorders may influence certain thrombophilia tests. It is a reasonable practice to always question a patient’s diagnosis of inherited protein C, S or antithrombin deficiency, and antiphospholipid antibody syndrome, until review of records and laboratory results has clarified that the timing of the testing was correct. In the experience of the author’s Thrombosis Clinic, quite a few patients inappropriately carry a diagnosis of having an inherited thrombophilia, particularly of protein S and protein C, antithrombin deficiency, and antiphospholipid antibody syndrome, as there tests were either obtained at the wrong time or misinterpreted. If tests were done with correct timing...
Postthrombotic syndrome is caused by an interplay of (1) damage of venous valves by the thrombus or by associated inflammatory mediators, and (2) impairment of venous return attributable to acute thrombosis and heparin therapy. Thus, the only conclusions that are possible at this time about this patient’s thrombophilia status are (1) that protein S deficiency and antithrombin deficiency have not been ruled out yet, (2) that antithrombin should be tested at a later time when the patient is not any more on heparin and the acuteness of the VTE episode is over (ie, after ca. 2 to 4 wk), and (3) that protein S should be retested once the patient is off warfarin.

The First Few Months

Postthrombotic Syndrome

Figure 5. Postthrombotic syndrome with chronic right leg pain and swelling, skin hardening, dryness, and itching and with postthrombotic (hemosiderin) pigmentation.

and results found to be low, repeat confirmatory testing at a separate time point to confirm the deficiency is advisable.

The patient presented here is heterozygous for factor V Leiden (Arg506Gln), the prothrombotic variant of factor V. Whether she also has inherited protein S or antithrombin deficiency is questionable. Estrogen-containing birth control pills and acute thrombosis often lower protein S levels. Low antithrombin levels may be attributable to acute thrombosis and heparin therapy. Therefore, the only conclusions that are possible at this time about this patient’s thrombophilia status are (1) that protein S deficiency and antithrombin deficiency have not been ruled out yet, (2) that antithrombin should be tested at a later time when the patient is not any more on heparin and the acuteness of the VTE episode is over (ie, after ca. 2 to 4 wk), and (3) that protein S should be retested once the patient is off warfarin.

Warfarin Management

Over the next few months the patient takes warfarin, monitored by her primary care physician’s office. A point of care INR monitor is used in the office that determines the prothrombin-time via a finger stick, which allows the patient to receive immediate INR results and, if necessary, instructions on further warfarin dosing, while she is still in the office. Because of significant INR fluctuations over time, her anticoagulation provider recommends that she take 2 multiple vitamin tablets containing a high content of vitamin K (such as 40 microgram per tablet) every day, as this has been shown to decrease INR fluctuations in some patients.

At 6 Months

Case Continuation

At 6 months follow-up she still has significant left leg calf pain and swelling, impairing her level of daily activity, in spite of wearing a compression stocking. Symptoms are worse at the end of the day and after standing on her feet for a prolonged period of time. She has completely recovered from a respiratory point of view. A Doppler ultrasound shows recanalized DVT in the left leg thigh with patent femoral and common femoral veins. Her physician is surprised by the extent of leg symptoms, given the relatively innocuous Doppler ultrasound findings, and suspects (1) venous obstruction proximal to the inguinal ligament, ie, in the iliac veins on the left side, or (2) venous insufficiency. An MRV scan (MRV = venous MRI scan) of the abdomen and pelvis (Figure 4) is obtained, which shows chronic occlusion of the left common and external iliac veins.

Chronic Postthrombotic Pelvic Vein Occlusion/Narrowing

Routine and sequential follow-up Doppler ultrasound examinations after an acute DVT are not indicated, as results typically do not lead to a change in management. However, reexamination can be considered if (1) discontinuation of vitamin K antagonist therapy is contemplated and the amount of residual venous obstruction is used as one of the predictors of recurrence, (2) anticoagulation is discontinued, so that a new baseline is established for further comparison in the future, in case new symptoms off anticoagulants were to occur, and (3) there is significant postthrombotic syndrome and the patient is evaluated for the feasibility of vascular intervention with pelvic vein angioplasty and stenting.

The patient presented here has chronic pelvic vein thrombosis as sequelae of her DVT and possibly attributable to preexisting May-Thurner syndrome. As the patient has quality of life–limiting leg symptoms, radiological intervention with angioplasty and stenting are discussed with her. A conventional contrast venogram is performed, with access of the deep venous system through the left posterior tibial vein. The left common femoral vein is patent, but there is total occlusion of the left external iliac and common iliac veins,
with prominent pelvic collateral veins seen that drain the blood from the left leg to the iliac veins on the right side. A catheter is pushed through the occluded vessel, angioplasty performed, and 3 stents deployed from the external iliac to the common iliac vein. Postangioplasty and stenting venogram reveals widely patent femoral, external iliac, and common iliac veins.

The patient has immediate improvement in her symptoms. She is kept on warfarin with a target INR of 2 to 3. On follow-up 3 months later she reports marked improvement, with only mild residual leg tiredness, but no pain, and only mild leg swelling.

Length of Warfarin Therapy

One of the major decisions in patients with VTE is how long to treat with anticoagulants. The risk-benefit assessment of continuing or discontinuing anticoagulation beyond 3 to 6 months of therapy depends on (1) the risk of recurrent VTE, (2) the risk of bleeding, and (3) the patient’s preference. Predictors of a higher risk of recurrence after a spontaneous ("idiopathic") VTE are: (1) male gender,21 (2) positive D-dimer test (determined either on or off anticoagulation22,23) after several months of anticoagulant therapy, (3) significant residual venous obstruction in the leg veins,24 (4) presence of a strong thrombophilia (antiphospholipid antibody syndrome; double heterozygote factor V Leiden and II20210 mutations; congenital deficiency of protein C, protein S, and antithrombin; possibly homozygous factor V Leiden), (5) recurrent VTE. A lower risk of recurrence is present if the initial VTE event (1) was associated with oral contraceptives, pregnancy, or hormone replacement therapy,25 (2) was only a distal, not a proximal DVT. Furthermore, patients with a PE as the first event have a higher case-fatality rate if VTE recurs. Predictors of a higher risk for bleeding are (1) older age, (2) fluctuating INRs, (3) history of bleeding. The bleeding risk decreases significantly if no bleed has occurred in the first 6 months of treatment.

The patient discussed here is thought to have a relatively low risk of recurrent VTE: (1) she is female, (2) her initial VTE was associated with an estrogen-containing birth control pill, (3) and she has a negative D-dimer while on warfarin. The fact that she is heterozygous for the factor V Leiden mutation may slightly increases her risk of recurrence.26 Whether the pelvic stents increase the risk of recurrence is not known. The patient and her physician decide to stop her anticoagulation, as (1) they consider her risk of recurrence to be relatively low, (2) she is well aware of the symptoms of DVT and PE and knows to seek early medical attention if such symptoms occur, (3) she knows to avoid estrogen-containing contraceptives, (4) she will avoid dehydration, (5) she is aware that she needs diligent VTE prophylaxis if she has major surgery, immobility, or trauma, and (6) she will consider taking an injection of low-dose low molecular weight heparin before long flights, such as flights of more than 5 h duration. Because she has 3 pelvic venous stents, her physicians empirically recommend that she take an aspirin (such as 81 mg per day) long-term, although they understand that it is not known whether aspirin has any benefit in preventing venous stent occlusion.

Long-Term Anticoagulation

In view of the fact that the patient is tolerating warfarin well, has 3 venous stents that may be thrombogenic, and is young and has a low risk of bleeding, it may also have been a reasonable choice for the patient to stay on warfarin long-term. In that case, consideration for using an INR home monitor would have been appropriate, as INR home monitoring compared to physician’s office INR monitoring has been shown to lead to better health outcomes: decreased recurrence of thrombosis, bleeding, and mortality.27 Follow-up at regular interval by her thrombosis physician would then have been appropriate for (1) clinical monitoring, (2) discussing newly published clinical studies that may impact her management, (3) informing her on ongoing clinical trials and offering her participation in these, and (d) encouraging her to become active, locally or nationally, in patient advocacy for people with thrombosis and thrombophilia.

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References

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