Picture Quiz: An Acute, Blue, Swollen, Painful Leg

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Keywords
Deep Vein Thrombosis, Phlegmasia Cerulea Dolens, Venous Gangrene.

Key Learning points
- Acute total or near total venous thrombosis of a limb may present with the clinical triad of swelling, pain and cyanosis (Phlegmasia cerulea dolens).
- In phlegmasia cerulea dolens, peripheral pulses may be absent and co-existent arterial insufficiency should be considered.
- Early imaging is vital to identify venous thrombus and exclude arterial insufficiency
- Phlegmasia cerulea dolens is associated with high morbidity and mortality and requires prompt intervention.
- Important complications to identify include systemic shock, pulmonary embolus, venous gangrene and compartment syndrome.

Answers

1. The differential diagnosis includes:
   - A. Arterrial occlusion
     - i. Embolic
       - a. atrial fibrillation
       - b. septic emboli
       - c. vasculitic
     - ii. Obstructive
       - a. atherosclerosis
       - b. extrinsic compression
       - c. (rarely arterial dissection)
   - B. Total venous outflow occlusion with tissue ischaemia ('phlegmasia cerulia dolens')
   - C. Prolonged exposure to cold
   - D. Trauma

The differential diagnosis broadens when considering acute onset painful, cold extremities to include Raynaud's disease and secondary causes of Raynaud's syndrome.

2. Duplex ultrasound to differentiate between venous occlusion and arterial insufficiency.
3. There is thrombus extending from the femoral vein up the inferior vena cave (IVC) to a level 1cm below the right renal vein (marked by the arrow in Figure 3). Bilateral pulmonary emboli were also present (not shown here).
4. Anticoagulation with intravenous heparin, fluid resuscitation, oxygen, and leg elevation. Catheter-directed or systemic thrombolysis and thrombectomy (surgical or percutaneous) should also be considered.



Figure 3. CT scan showing thrombus in the inferior vena cava to the level of the right renal vein.

5. Investigation for underlying causes should be guided by careful history, examination, chest X-ray, urinalysis and routine laboratory testing (including full blood count, serum calcium and liver function tests). If no predisposing factors are identified then abdomino-pelvic CT scan should be considered in view of the association with underlying malignancy. A mammogram should be considered in female patients. The presence of a predisposing hypercoagulable state may be identified during the history. National Institute for Health and Clinical

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Excellence (NICE) guidelines[1] recommend consideration of testing for antiphospholipid antibodies in unprovoked DVT or PE if it is planned to stop anticoagulation treatment.

Case Outcome

Urgent Duplex ultrasound demonstrated ilio-femoral deep vein thrombosis (DVT) with involvement of the long saphenous and short saphenous superficial veins. Arterial Doppler waveforms were normal distally with no evidence of stenosis. The diagnosis was therefore Phlegmasia cerulea dolens (PCD), resulting from an extensive, proximal DVT with total or near total venous outflow occlusion.

Anticoagulation with intravenous infusion of unfractionated heparin, fluid resuscitation and leg elevation were commenced. The patient was monitored for signs of complications including systemic shock, venous gangrene and compartment syndrome. Graduated compression stockings were fitted after 7 days to reduce the risk of post-thrombotic syndrome and the patient was discharged from hospital for 6-months duration of anticoagulation with warfarin.

Careful history, examination, urinalysis and routine laboratory testing did not identify a predisposing cause for PCD.

CT scan undertaken to confirm the extent of the thrombus confirmed there was no radiological evidence of underlying malignancy. Good views of the pancreas and pelvic organs were obtained.

Discussion

Phlegmasia cerulea dolens (previously called "blue phlebitis of Gregoire")[2] is the clinical triad of pain, oedema and cyanosis of a limb caused by a large, usually proximal deep vein thrombosis (DVT). The precipitating thrombus causes near-total occlusion of collateral as well as deep veins, thus impairing venous return. There is a consequent rise in hydrostatic pressure which causes massive fluid extravasation, clinically manifesting as interstitial oedema and hypovolaemic shock.[3] Arterial insufficiency and venous gangrene may follow.[4] Pulmonary emboli (PE) are commonly present at time of diagnosis.[3] If superficial veins remain patent then the less severe phlegmasia alba dolens will be present though this may progress to PCD.[5] Phlegmasia alba dolens is characterised by a blanched, pale, swollen, painful limb without the cyanosis present in PCD.

PCD is an important, but rare presentation of deep vein thrombosis. Any delay in recognition or treatment can have grave implications for limb viability and patient mortality.[6] In a systemic review of 62 cases of PCD between 1980 and 2008,[6] overall mortality was 26% and major amputation 14%. The presence of venous gangrene worsened the prognosis.

The initial presentation can be similar to that of an ischaemic limb[7] as the leg is cool and cyanotic rather than warm and red. Additionally, peripheral pulses can be difficult to palpate, as in this case, due to the substantial oedema. PCD is uncommon in the upper limb, and there is preponderance for the left lower limb,[6, 7] possibly due to the anatomical course of the right common iliac artery overlying the left common iliac vein.[8]

Differentiation between venous occlusion and arterial insufficiency requires early imaging to identify the location and extent of any obstruction and to verify distal arterial flow. Coexistant venous and arterial occlusion may occur. Urgent duplex ultrasound (USS) is generally preferred as noninvasive first line investigation if available, followed by cross sectional imaging.[6] Duplex ultrasound has a high degree of sensitivity and specificity for venous thrombosis, and can also identify distal arterial flow.[9] Other imaging modalities include conventional contrast venography, computed tomography or magnetic resonance venography. Advantages of invasive/contrast imaging modalities include the potential for invasive intervention (catheter-directed thrombolysis, venous thrombectomy, IVC filter insertion), and for identifying the proximal extent of thrombus, potential complications of PCD, and underlying aetiology. Non-invasive physiological testing using the ankle-brachial pressure index (ABPI) assists with differentiation of arterial from other causes of the acutely cold, painful limb, but should not delay more definitive imaging.

Treatment of PCD should be prompt, aggressive and directed towards reducing the thrombus load, preserving the patency of collateral circulation, preventing propogation of the thrombus, and correcting any hypovolaemia. Initial treatment usually includes intravenous heparinisation, fluid resuscitation and leg elevation to encourage venous return.[3] In many cases, this is all the treatment that is required.[10] The use of low molecular weight heparin in PCD has not been rigorously studied. Chinsakchai et al.[6] provide a comprehensive literature review of the evolution of management and therapeutic options. Second line treatment strategies such as surgical thrombectomy and fasciotomy, catheter directed thrombolysis (CTD) and percutaneous mechanical thrombectomy (PMT) and should be guided by severity at presentation on a case-by-case basis with vascular surgical and radiology input. Minimally invasive techniques such as CTD and PMT may be more suitable than surgical thrombectomy to maintain viable tissue.[6, 11]. IVC filter insertion may help prevent embolisation to the pulmonary circulation although there have been case reports of IVC filter associated PCD.[12, 13] In this case, the proximity of the thrombus to the right renal vein would have only allowed for IVC filter placement above this level with the risk of renal vein thrombosis. Surgical and systemic thrombolytic therapy was considered but not required in view of the patient's rapid response to first line therapy.

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Complications of PCD may be local, or systemic. The earliest descriptions of PCD were in association with venous gangrene. Venous gangrene remains the most common local complication if treatment of PCD is delayed. It tends to begin distally, and may result in the need for amputation.[3, 6, 7] With massive fluid extravasation, compartment syndrome may also develop. Common systemic complications of PCD include hypovolaemic shock, propagation of the thrombus, pulmonary emboli and post thrombotic syndrome.

As with other thromboembolic disease, malignancy is a precipitant of PCD, being present in a third of patients.[6] Cases of PCD have been described as early or late complications after insertion of IVC filters.[12, 13]

There are no evidence based guidelines for the management of Phlegmasia cerulea dolens or Phlegmasia alba dolens. Within the UK, NICE Clinical Guideline 144 advises on the management of venous thromboembolic disease[1]. Recommendations are made for the treatment of symptomatic iliofemoral DVT but no reference is made to these rare, emergency situations.

It is important for the acute physician to be aware of such venous thromboembolic emergencies as the need for prompt recognition and appropriate intervention is paramount.

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