
A Dilemma in Anticoagulant Therapy

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A man of 67 years was seen as an emergency with a high swinging fever, suprapubic and bilateral loin pain and the passage of foul smelling urine which contains gas. He had obviously lost weight over several months and had a 6 month history of a change of bowel habit with fresh blood and mucus in his stool.

Question 1: What are the probable clinical diagnoses and what has caused the presenting symptoms?

Answer: This man has a fistula between the gut and the urinary tract. This was confirmed to be a colovesical fistula by barium enema, colonoscopy and cystoscopy. As a result of the passage of faecal matter into the urinary tract, he had developed a bilateral ascending pyelonephritis and septicaemia (*E. coli* was

cultured from his blood). The background disease was a colonic neoplasm which had spread locally into the bladder. Ultrasound showed a single metastasis in the right lobe of the liver. The infection was controlled by antibiotic therapy.

Laparoscopy showed extensive tumour spread within the pelvis, and local resection was not possible. A colostomy was carried out at the level of the descending colon and radiotherapy was given to the pelvis. This resulted in dramatic shrinkage of the tumour mass and improvement of the symptoms of the colovesical fistula and he was discharged home. Ten days after completing his radiotherapy the patient called his family doctor because of pain in his left thigh and calf (Fig. 1).

The patient's legs on re-admission to hospital.



Question 2:

- (i) What is the likely cause of this pain?**
- (ii) What risk factors for the likely cause of the pain are present in this man?**
- (iii) What investigation is required to establish the diagnosis?**

Answer:

(i) The likely diagnosis is deep venous thrombosis (DVT). Local pain over thrombosed deep veins is found in about 50

per cent of cases of DVT in the calf and about 70 per cent when the DVT is more proximal but it is important to remember that some cases of DVT are completely asymptomatic. As shown in **Fig. 1** the leg was swollen with an increased circumference of both the thigh and calf. There was also pitting oedema on the dorsum of the foot. There were visible superficial veins in the affected limb on the calf and thigh. The affected limb was redder than the other and it was warmer, up to the

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groin, than normal. Doctors should be actively discouraged from assessing for 'Homan's sign' by dorsiflexing the foot, because of the very real danger of dislodging emboli and because

the test gives no additional information. Other possible symptoms and signs are shown in **Table I.**

Table 1: Possible clinical features of DVT.

Symptoms	Signs
Swelling and tightness	Swelling with some pitting oedema on the dorsum of the foot/ankle
Tenderness to touch or movement	
Cramping pains in the calf or thigh (usually in one leg)	Pain in the calf on gentle compression in the popliteal fossa and along the line of the femoral vein
Discoloration, ranging from white to purple	Colour changes Increased temperature in the whole limb Dilation of superficial veins, particularly at the ankles Signs of pulmonary embolism
No symptoms in the legs: - presentation with pulmonary embolism - sudden death - detected in a screening test	No signs - the patient had been diagnosed by a screening test (usually carried out because the patient is at high risk)
The symptoms and signs of DVT are extremely variable and in about 50 per cent of patients no symptoms or signs are present; some of these patients will have no sequelae, but some present with pulmonary embolism or, much later, with post-phlebitic syndrome. As a general rule the more proximal the thrombus the more likely it is that symptoms and signs are present. The key is to be suspicious in a patient with multiple risk associations and to perform a simple screening test such as ultrasound as a routine in high risk patients.	

(ii) The clinical risk factors for DVT in this man are;
 (a) Age (67 years)
 (b) Recent infection
 (c) Presence of advanced cancer, especially in the pelvis
 (d) Immobility following surgery
 (e) Radiotherapy producing tissue breakdown of tumour
 (f) In addition his plasma fibrinogen was recorded at 4.8g/l, which is extremely high and reflects the recent infection, the presence of cancer and the tissue necrosis following radiotherapy. Plasma fibrinogen

is an important laboratory predictor of DVT. A range of other possible risk factors is shown in **Table 2.**

(iii) The preferred investigations for diagnosis of DVT are ultrasound and venography. The 'gold standard' test is venography, but this has the disadvantages that it is invasive, uncomfortable for the patient and time consuming. It is, however, sensitive and specific. Ultrasound is rapid, repeatable and cheaper, but it is much more operator-dependent, and therefore less sensitive and specific.

Table 2: Risk associations for DVT.

Age	DVT is unusual before 40 years of age but becomes progressively more common with advancing age
Obesity	Best measured by body mass index (BMI)
Surgery	Associated with immobility and tissue damage, for example, trauma, burns, etc. The incidence of DVT is 70 per cent following surgery for fractured neck of femur and 30-40 per cent following routine alimentary surgery
Malignancy	Often gastrointestinal or gynaecological, but most tumours have been associated. Tissue breakdown associated with radiotherapy or chemotherapy leads to additional risk
Immobility	As a result of splinting for fractures, stroke, paraplegia or any other severe medical or surgical disorder
Inflammation	Especially chest infections, inflammatory bowel disease and cholecystitis. Also after acute myocardial infarction, possibly because of tissue necrosis with an inflammatory response
Increased venous pressure/ decreased return	Results in reduced venous flow and is associated with heart failure, shock, peripheral vascular disease and pregnancy
Oestrogens	In higher dose oral contraceptive users, men receiving oestrogen (for example, prostatic carcinoma)
Haematological and biochemical abnormalities	Including polycythaemia, cryoglobulinaemia, thrombophilic states (protein C, S and antithrombin III deficiencies) and homocystinuria
Numerous clinical risk associations have been described and given 'scores' reflecting their importance, and various mathematical formulae have been produced, which can be used as predictors. The age and degree of obesity of the patient are the most important followed by the extent of the surgery to be carried out (all operations lasting over 30 minutes put the patient at special risk). The presence or absence of these factors before surgery allows for the classification of patients into high, medium and low risk and this determines the type and duration of prophylaxis to be given.	
In this particular man the risks were, age (67 years), surgery, presence of disseminated cancer, radiotherapy, recent infection and immobility.	

Question 3: Venography was carried out and the films are shown in Fig. 2. Describe the abnormalities seen.



Fig. 2: Venogram of the left leg at three levels: knee, thigh and inguinal region.

Answer: Contrast was injected into the veins of the dorsum of the foot and followed on the screen as it travelled into the deep vein system. This is done by applying and releasing a tourniquet at the ankle. In the first picture there are small filling defects in the network of communicating veins just below the knee. In the central X-ray the contrast has not continued in a main vein above the mid-thigh and has flowed into a collateral network of veins, suggesting an obstruction in the femoral vein in Hunter's canal. In the third view there has been some return of diluted contrast into the proximal femoral vein, which also has more proximal filling defects.

The investigation confirms the presence of small thrombi in the calf and a major occlusive thrombus in the femoral vein.

Question 4: What is the optimal treatment of established proximal vein thrombosis?

Answer: Anticoagulation should be established with a bolus of intravenous heparin (5,000i.u.) and continued initially with an infusion of heparin at the rate of 20,000 units per 12 hours. This rate of infusion must subsequently be controlled by measurement of the activated partial thromboplastin time (APTT) to ensure that this test is prolonged by 2-2.5 times that of a control.

Question 5: What treatment, if any, should be offered for this patient's venous thrombosis?

Answer: This patient presents a major medical, moral and ethical dilemma. With a venous thrombus of this size and position the possibility of a major or fatal pulmonary embolism is extremely high (probably 10-20 per cent). However, the colonic cancer and fistula might both be sources of haemorrhage if he were anticoagulated. An alternative to the use of anticoagulant is to insert a vena caval filter to prevent the upward migration of emboli. The deciding factor was that despite the presence of metastatic and locally invasive tumour his general health and well-being were extremely good and he apparently had the potential to have a period of good quality life with a very devoted family. The various options were discussed with the patient and his family and it was decided that anticoagulants were to be the first option, with careful control of dosage and careful observation of blood values and any blood loss. The heparin regime

discussed above was started, and the patient was also started on a smaller than usual dose of warfarin (5mg stat and 5mg at 24 hours) for long term anticoagulation.

Question 6: How should the dose of warfarin be controlled and for how long should it be given?

Answer: In this patient tight control was necessary because of the possibility of colonic bleeding and this was done by measuring the International Normalized Ratio (INR) and maintaining it at a value of 2-2.5. The duration of therapy should be of the order of 3 months.

COMMENT

Deep vein thrombosis is the commonest cause of preventable death in Western medicine. In individual patients the actual cause is often not determined, but a list of risk associations is now well accepted and all patients admitted to hospital medical, surgical, and gynaecological wards should be assessed to determine whether they are at risk (Table 2).

If they are at risk and there is no contraindication then some form of prevention of DVT should be offered. This will depend on the classification of degree of risk.

No prophylactic regimens had been offered to this man for his initial laparoscopy and colostomy because of the short duration of surgery. The subsequent development of a proximal vein thrombosis was the result of a series of interacting factors.

The clinical diagnosis of DVT is difficult as the symptoms and signs are so variable. Clinical suspicion should lead to performance of an appropriate investigation so that the other pathologies which mimic DVT symptoms and signs are eliminated (Table 3).

If there are no contraindications (see Table 4) then the treatment of choice is anticoagulants. As anticoagulants have a high incidence of bleeding side effects, the importance of a positive diagnostic test cannot be overstated - i.e. a thrombus must be demonstrated before long term anticoagulant treatment is embarked on. The duration of well controlled anticoagulation should be between 3 and 6 months depending on the extent and position of the thrombus and the presence of emboli.

Table 3: The differential diagnosis of deep vein thrombosis.

Muscle strain and haematoma
Arthritis/synovitis/joint trauma
Baker's cyst
Varicose veins
Infection, with cellulitis/lymphangitis
Lymphatic obstruction, usually as a result of tumour
Swelling caused by the loss of muscle pump action in a paralysed limb
Oedema caused by heart failure, liver disease, nephrotic syndrome
Postphlebotic syndrome
These conditions may mimic the features of deep vein thrombosis. They should be excluded by appropriate investigations but it should be remembered that DVT may coexist, especially in ruptured Baker's cyst and muscle and tendon rupture. It is therefore often advisable to carry out ultrasound examination of the veins at the same time.

Table 4: Contraindications and cautions in the use of anticoagulants.

Current or recent (6/12) internal bleeding
Potential bleeding site e.g. peptic ulcer, varices, ulcerative colitis
Known bleeding disorder e.g. severe liver or renal disease
Recent stroke (6/12)
Severe uncontrolled hypertension
Haemorrhagic retinopathy (e.g. diabetic)
Endocarditis
Recent organ biopsy
Known allergy to drugs (heparin/warfarin)
Concomitant requirement for aspirin/NSAIDs
