J R Coll Physicians Edinb 2011; 41:18–21
doi:10.4997/JRCPE.2011.105

CLINICAL

'No DVT found' is not a diagnosis: look beyond the D-dimer

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ABSTRACT Current clinical practice is often heavily biased towards the exclusion of potentially serious, treatable diagnoses, such as deep venous thrombosis, rather than the positive diagnosis of the patient's underlying illness which precipitates seeking medical attention. We report a case of leg swelling where deep venous thrombosis was repeatedly excluded as a cause of leg pain and swelling, but where arrival at the correct diagnosis was significantly delayed, in part due to protocol-driven practice.

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KEYWORDS Clinical acumen, leg swelling, Paget's disease of bone

DECLARATION OF INTERESTS No conflict of interests declared.

INTRODUCTION

The diagnosis of lower limb deep venous thrombosis (DVT) can be challenging. The need for accurate diagnosis is based on the concern that failure to diagnose DVT may lead to the possibility of potentially fatal pulmonary embolism. Venous thromboembolism, along with chest pain, heart failure and a number of other common medical conditions, has been subject to the introduction of clinical algorithms to confirm or exclude the presence of a particular diagnosis. Most algorithms employ the use of a clinical scoring system linked to a serum biomarker to increase the likelihood of correctly excluding or confirming the diagnosis in question.[1]

In the case of DVT, the clinical risk evaluation is undertaken using the Wells score (Table 1). This screening questionnaire establishes a pre-test likelihood of the presence of an underlying DVT, and this is used in conjunction with the measure of plasma D-dimer concentrations to determine whether or not there is a low risk of DVT. D-dimer is a fibrin degradation product resulting from the spontaneous fibrinolysis associated with intravascular thrombosis. While an elevation of D-dimer is common to a number of clinical situations, a low D-dimer concentration is regarded as likely to exclude the presence of venous thromboembolism.[1]

This method relies on the application of Bayesian principles of conditional probability; principally that the less likely the person is to have a DVT the more the presence of a normal D-dimer enhances the predictive value of the combined assessments in excluding the presence of a DVT. If, however, the pre-test Wells score is not in the low probability of DVT range, the ability of D-dimer to exclude DVT is weakened and another test is required to confirm or refute the presence of DVT.

TABLE 1 Wells clinical prediction rule for deep venous thrombosis (DVT)[2]

Clinical feature	Points
Active cancer (treatment within 6 months or palliation)	1
Paralysis, paresis or immobilisation of lower extremity	1
Bedridden for >3 days because of surgery (within 4 weeks)	1
Localised tenderness along distribution of deep veins	1
Entire leg swollen	1
Unilateral calf swelling of >3 cm (below tibial tuberosity)	1
Unilateral pitting oedema	1
Collateral superficial veins	1
Alternative diagnosis as likely as or more likely than DVT	–2
Total points	

Risk score interpretation (probability of DVT):

- ≥3 points: high risk (75%)
- 1–2 points: moderate risk (17%)
- <1 point: low risk (3%)

The application of these measures will determine the necessity for a compression ultrasound of the lower limbs. Clearly, it is imperative to employ the Wells criteria extremely carefully to accurately define the pre-test likelihood of DVT before performing a measurement of D-dimer, as this may significantly influence the outcome of the evaluation.

At this stage the outcome is effectively binary, namely DVT: yes or no. The former outcome will lead to the consideration of anticoagulant therapy and potential further investigations to identify a possible predisposing reason for thrombosis. The latter will be met with reassurance that there is no potentially life-threatening

TABLE 2 Medical history and current medication

Medical history
Mild proliferative glomerulonephritis (1991) Acute gout (1996) Angina pectoris (2001) Chronic kidney disease stage 3B (2009)
Current medication
Candesartan, 4 mg once daily Isosorbide mononitrate (slow release), 60 mg once daily Aspirin, 75 mg once daily Simvastatin, 40 mg once daily Atenolol, 50 mg once daily

TABLE 3 Summary of DVT service actions in the 24 months before diagnosis

	Pre-test assessment	**D-dimer** (normal range: 0–230 ng/ml)	**Doppler ultrasound scan result**	**Post-test assessment**	**Serum alkaline phosphatase** (normal range: 40–125 U/l)	**Final diagnosis**
Visit 1	Moderate probability	54	No evidence of DVT	No DVT	234	No DVT, reassure
Visit 2	Moderate probability	113	No evidence of DVT	No DVT	354	No DVT, osteo-arthritis of knee
Visit 3	Moderate probability	85	No evidence of DVT	No DVT	481	No DVT, reassure

thrombosis present. This is, however, incomplete and potentially unsatisfactory in explaining the symptom or symptoms that caused the patient to seek medical advice in the first instance.

We report a case where this approach was repeatedly taken and no positive diagnosis was made until two years after the initial consultation.

CASE REPORT

A 64-year-old white male was referred to a general medical outpatient clinic because of pain in his right lower limb. The pain had been present for at least two years before the referral and the patient had been seen in a hospital emergency department on three separate occasions during that time.

The patient's medical history and prescribed medication are listed in Table 2. At the time of the onset of pain in his right leg, there were no other active medical issues. On each occasion, the patient described a deep boring pain encircling the right leg from the knee to the mid-calf, associated with a paroxysmal 'tightening' of the leg. On each occasion, the leg was described as swollen, hot to the touch and red by the practitioners who saw him. The likelihood of an underlying DVT was assessed as moderate on each occasion, and the patient had a full assessment by the local hospital DVT service (Table 3). During this time, he had a number of other blood tests performed as part of 'routine bloods'.

Of note during this time is the persistent elevation of the serum alkaline phosphatase measurement in the absence of any other derangement in bilirubin, transaminases or gamma-glutamyl transferase. Indeed, serum alkaline phosphatase had been elevated for five years prior to the patient's first attendance at the DVT service. At no time during this period was either plain radiography of the skeleton or ultrasound examination of the liver undertaken.

Figure 1 (overleaf) shows the appearance of the patient's right leg at the time of the outpatient assessment. The appearance is highly suggestive of Paget's disease of bone, with the typical appearance of pseudo-bowing of the tibia present. The skin was locally warm to the touch and shiny in appearance. Figure 2 reveals the plain radiographic appearance of the right tibia. The radiological appearances are classical of Paget's disease of bone, in particular the coarse trabecular texture of the proximal tibia and the loss of cortico-medullary differentiation giving way to normal bone architecture in the distal tibia. A triple-phase isotope bone scan was performed, which confirmed the localised extent of Paget's disease in the right proximal tibia.

Following diagnosis, the patient was treated with oral risedronate, 35 mg once daily, for two months, with excellent clinical and biochemical response.

DISCUSSION

Paget's disease of bone is estimated to affect 3–5% of the population over the age of 55 and the prevalence rises steeply with age.[3] Typically the pelvis or femora are affected, but the tibia and skull are other common sites of occurrence. More than 80% of individuals experience pain localised to the affected bone and the tibia is the most common site of fracture.[4,5]

The classic clinical description of the tibia affected by Paget's disease is that it is bowed, expanded anteriorly and laterally, and hot to the touch. Often the skin is described as shiny and dilated superficial veins may be noted.

The Wells criteria for the pre-test assessment of likelihood of lower extremity DVT could easily be used to assign a score of 2 or 3 to our patient: one point for

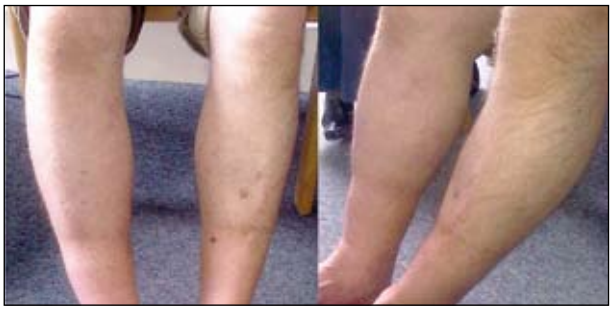

FIGURE 1 Clinical photograph of both lower limbs showing typical features of Paget's disease of bone localised to the upper right tibia.

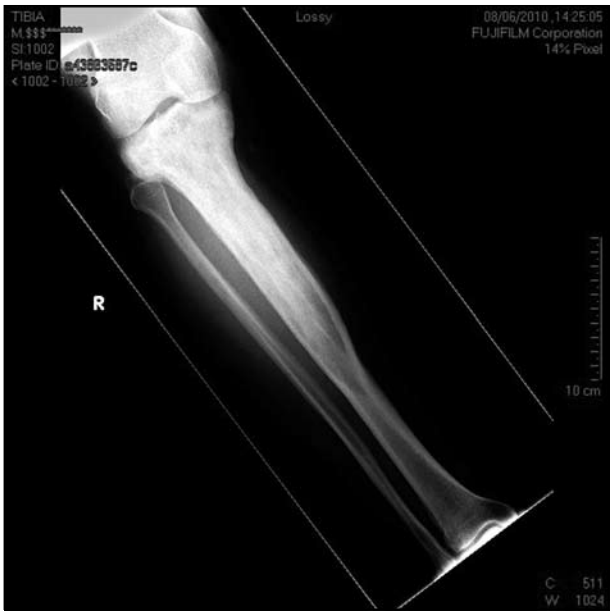

FIGURE 2 Plain radiograph of the right tibia and fibula displaying the typical features of localised Paget's disease of bone in the proximal right tibia.

unilateral calf swelling, one point for unilateral pitting oedema and possibly one point for collateral superficial veins,[2] particularly if clinical examination is limited or undertaken by someone with limited experience or skill in the interpretation of clinical signs. If an elevated Wells score is determined, then a measurement of D-dimer will be undertaken as part of the diagnostic algorithm. In this case, on three occasions a negative D-dimer was obtained, a compression ultrasound performed and DVT was excluded. However, on each occasion there was no satisfactory explanation provided for the patient's symptoms and signs. Furthermore, important clinical information was obtained but overlooked. This would have influenced this patient's diagnostic evaluation and subsequent management.

While to our knowledge there are no data to suggest that D-dimer concentrations are elevated in the presence of monostotic or polyostotic Paget's disease, there are clear guidelines for the investigation of persistently abnormal liver function tests, especially alkaline phosphatase.[6]

This approach of using a protocol to confirm or exclude a single diagnosis based on the exclusion of a single pathology raises two issues that require careful consideration:

- The Wells criteria include the question 'is an alternative diagnosis likely?' with an associated score of –2. This can effectively lower the pre-test probability score to the low-risk category in many cases but relies on the judgement and experience of the individual assessing the person with suspected DVT.[7]
- Once DVT has been excluded there may be no clear diagnostic pathway to arrive at an alternative positive or 'correct' diagnosis to explain the symptoms that led to the patient's initial presentation.

In this case there are two areas that highlight the potential for this approach to fail individual patients. Firstly, the repeated presentation with identical symptoms and signs that repeatedly generate the same investigations and findings should have raised the possibility of an alternative diagnosis underlying the patient's presentation. Secondly, the failure to recognise and act on the collateral information, namely the progressively rising isolated alkaline phosphatase, was clearly detrimental to the patient's diagnostic journey. The raised alkaline phosphatase not only raises the possibility of an alternative diagnosis and thus alters the Wells score, it should ring alarm bells as to locally important clinical problems in this context.

CONCLUSION

While the exclusion of DVT is important insofar as it allows an individual to be reassured that they do not have a DVT and that the risk of associated pulmonary embolism is extremely low, it does not answer the question being asked by the patient. Such diagnostic algorithms are vital tools in assessing patients in busy acute medicine units or accident and emergency departments; they rely, however, on the unspoken truth that the people assessing the patients know what they are doing. The ability of the patient's assessor to use the score confidently and find other likely causes for limb swelling is crucial to driving the subsequent workload. The ease by which a low pre-test probability can be converted into a moderate risk will inevitably increase the number of D-dimer measurements and requests for compression ultrasound. Repeated presentation with the same clinical problem should raise the possibility of another underlying problem, and referral to other specialties should be considered if appropriate. Furthermore, if other investigations are requested and found to be abnormal, appropriate action should be taken.

Accordingly, there is still a place for clinical acumen in the management of isolated lower limb swelling, especially if repeated assessments exclude DVT in the presence of persisting symptoms and abnormal clinical signs.

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