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A DISCONCERTING LEG: A CASE OF DEEP VEIN THROMBOSIS WITH NEGATIVE D-DIMERS

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ABSTRACT

The annual incidence of deep vein thrombosis (DVT) in the general population in France is about 1% to 1.6%. It can occur without triggering factor identified or in patients with risk factors. We report an original case study of a patient with DVT of the lower limb proven despite a negative D-dimers rate and low predictive score.

When the predictive score of venous thromboembolic disease is low, the diagnostic strategy is that D-dimers are assayed for eliminating DVT, the negative predictive value being very high, around 94% to 100%. The use of Doppler ultrasound is then recommended. The cases of false negatives reported in the literature are few and question the false negative D-dimers etiologies.

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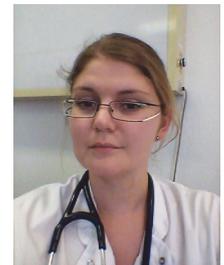
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CLINICAL CASE

We report the case of a 32 year old athletic man, presenting himself to medical consultation in general practice for pain in the right calf lasting for one week. The only medical history he presented was a meniscectomy of the right knee six months ago without prolonged immobilization and an episode of left cervical-brachial neuralgia.

The clinical examination revealed a hemodynamically stable patient, his blood pressure was 123/68 mmHg, with a heart rate of 66 beats per minute, a respiratory rate of 14 cycles per minute and a temperature of 36.3° Celsius. Examination of the lower limbs area highlighted soft calves with no loss of lateral movement or increase in circumference. Pain on palpation of the internal right gastrocnemius muscle, exquisite and consistently reproducible

was present with a negative Homans' sign. The rest of the routine general examination was normal especially the cardiorespiratory exam (no right or left signs).

A venous echo-doppler of lower limbs was performed despite the low probability of DVT (Wells score = -2) [1] (**Table 1**) as well as a negative D Dimers blood level equal to 443 ng.mL⁻¹ using immune-enzymatic assay (negativity < 500 ng.mL⁻¹ according to laboratory standards).

Echo-Doppler revealed an internal gastrocnemius muscle thrombosis in the right leg. A conventional treatment [2] was then set up by low molecular weight heparin (LMWH) then relayed by oral anticoagulants anti-vitamin K type (AVK).

Predictive factor	Score
Active cancer (treatment within the previous six months or currently receiving palliative treatment)	1
Plaster or paralysis of the lower extremities	1
Recently bedridden for 3 days or more, or major surgery within the previous 12 weeks requiring general or regional anesthesia	1
Localized tenderness along the deep venous system	1
Entire leg swollen	1
Calf swelling at least 3 cm larger than that on the symptomatic side (measured 10 cm below tibial tuberosity)	1
Pitting edema confined to the symptomatic leg	1
Collateral superficial veins (non-varicose)	1
Previously documented deep-vein thrombosis (DVT)	1
Alternative diagnosis at least as likely as deep-vein thrombosis	-2
A score < 2 indicates that the probability of DVT is unlikely	
A score ≥ 2 indicates that the probability of DVT is likely	

Table 1: Modified Wells criteria [1]

DISCUSSION

The sensitivity and negative D-dimers levels are very high, between 94% to 100% [3] in the diagnosis of DVT in «all comers» patients and 100% in patients with predisposing factors [4;5] (Table 2). With low predictive score of DVT according to the modified Wells score and negative D-dimers, has our patient had a real DVT?

False negative results are rare with a sensitivity most frequently reported in the literature from 90 to 99% [6]. Kraaijenhagen et al. [7], in a european multicenter prospective study, had observed 2067 patients with clinical suspicion of venous thromboembolic disease (pulmonary embolism or DVT of the lower limbs). DVT of the lower limbs was objectified by Doppler ultrasound in 472 patients (prevalence = 22%) and 27 of these patients (or 4.6%) had negative levels of D-dimers (SimpliRED® Test). Although the results were not significant, the false negative rate was greater when a preventive treatment with LMWH was administered or when the consultation period after the first symptoms was longer than 10 days.

Cases of false negatives within the specific context of post-traumatic DVT when managed at an early stage are commonly reported, but according to Wahl et al. [8], D-dimers eventually always becomes positive (100%) after four days. The study of Wahl et al. prospectively included all patients with severe trauma with potential hospitalization period higher than three days. All benefited from lower limbs and D-dimers assays at regular intervals (3rd-4th day, 7th day then on weekly basis until hospital discharge). Authors have concluded that all patients admitted in the context of severe trauma and thromboembolic disease with clinical signs should be considered at high risk as long as D-dimers levels at day 4 are not negative (negative predictive value = 100%).

Plasma D-dimers levels seems to persist for a week after the thromboembolism episode [9;10] despite the implementation of an anticoagulant therapy. In some cases, such as patients with active cancer, calculating Wells score is less reliable [11]. Meta-analysis of Geersing et al. [9] was used to analyze the reliability

of Wells score and D-dimers assay. The authors analyzed thirteen studies that collected data on around ten thousand patients, 19% of whom having a proximal DVT. In accordance with what was expected, the highest Wells scores were associated with a higher probability of DVT (Table 3). A low Wells score (< 2) alone does not allow to satisfactorily eliminate a DVT. A combination of low Wells score with negative D-dimers was associated with an extremely low probability (1.2%) of DVT (95% CI: 0.7 to 1.8).

1. Transitory factors

- Recent surgery: orthopedic, major abdominal surgery, neurosurgical
- Traumatology: fracture of lower extremities < three months, prolonged immobilization
- Immobilization > three days: cerebrovascular accident stroke, sepsis, respiratory or heart failure, etc.
- Obstetrics: pregnancy, postpartum
- Gynecology: oestrogen-progesterone oral contraception (especially 3rd and 4th generations)
- Prolonged travel > five hours

2. Persistent factors

- Cancer: active or treated, myeloproliferative disease, chemotherapy
- Previous history of venous thromboembolism
- Constitutional thrombophilia: factors II and V mutations, protein C, S and antithrombin deficiency, factor VIII rise
- Acquired thrombophilia: antiphospholipid syndrome
- Inflammatory diseases: lupus, nephrotic syndrome, inflammatory bowel disease, Behcet's disease
- General characteristics: age > 65 years, obesity (BMI > 30)

Table 2: Predisposing factors for venous thromboembolism [5]

These results were valid regardless of the sub-groups: type of D-dimers assays (quantitative or qualitative), sex and support location (general practice or hospital). In the subgroup of patients with cancer, low Wells score associated with a rate of negative D-dimers was not reliable enough to eliminate a DVT. However, only the modified Wells score was reliable to eliminate DVT in the subgroup of patients with a history of DVT. Owaidah et al. [4] have evaluated the utility of combining D-dimers assay with a clinical pretest probability score in predicting DVT by physicians taking residence in the city. This work concluded that a pre-test score was a valuable tool to improve the detection accuracy of DVT, but also pulmonary embolism. However, in low predictive score, hinge value of positive D-dimers to retain was 250 ng.mL⁻¹ [4]. The absence of standardization of international calibrators for D-dimers assays and the variation in the de facto measurement units is a problem that should be highlighted. Taira et al. [12] studied the D-dimers cut-off levels, (that is to say between 200 and 500 ng.mL⁻¹) concluding that they would be reliable for low-risk patients with no need for further investigations.

A case of DVT with low predictive score with negative D-dimers is rare. In such case, the confirmed presence of DVT can be explained by a delayed consultation period from the onset of pain. While most studies agree that the combination Wells score and D-dimers assay is an excellent diagnostic tool for DVT, the analysis of cases of false negative D-dimers would perhaps highlight predisposing factors for this false negativity.

Wells score	Percentage of DVT probability (95% confidence interval)
-2	5.7 [3.6 ; 8.8]
-1	8.6 [5.8 ; 12.4]
0	12.8 [9.2 ; 17.5]
1	18.6 [14.0 ; 24.3]
2	26.3 [20.4 ; 33.2]
3	35.8 [28.3 ; 44.0]
4	46.5 [37.3 ; 55.9]
5	57.5 [46.9 ; 67.9]
6	67.9 [56.5 ; 77.5]
7	76.7 [65.5 ; 85.2]
8	83.7 [73.4 ; 90.6]

Table 3: Deep vein thrombosis (DVT) probability according to Wells score [7]

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