Diagnostic challenge of D-Dimer negative Upper Extremity DVT

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1. Background

Upper Extremity DVT (UEDVT) is an uncommon presentation with an incidence rate of 4-10%. [1] Studies suggest D-Dimer has a high sensitivity with negative predictive value for UEDVT, where sensitivity is around 92% with a negative predictive value of 98%.

Paget Schroetter Syndrome is a well-recognised form of UEDVT, namely, thrombosis of the axillary and subclavian veins induced through mechanical effort compressing the subclavian vein at the thoracic outlet.[2]

Constans score or Constans criteria, is a 2 level scoring tool first published in 2008. *Criteria considered; 1. venous material insitu, 2. localised pain, 3. unilateral oedema and 4. plausibility of alternative cause*. **Score interpretation; -1 to 0 points (low probability of UEDVT 12%), 1 point (intermediate probability 20%), 2 to 3 points (high probability 70%).** [4]

Kleinjan et el, sought to **further improve** upon this scoring tool by **incorporating D-dimer** results in the **stratification of intermediate risk patients**, asserting that its use can safely and effectively exclude venous thrombosis of the upper extremity.[8]

2. Case A

46y/o female; no significant past medical history. Presented with four day history of right arm swelling. Mild tenderness over forearm and upper arm. Superficial venous congestion around the shoulder and patient felt axilla was more prominent. Two weeks prior to presentation patient reported moving a wardrobe possibly provoking muscle injury over chest wall and arm.

Constans Criteria score 1

D-Dimer normal (159 ng/ml) (Reference range 0-250ng/ml).

High clinical suspicion for UEDVT despite scoring tool and D-Dimer result.

Right upper limb US Doppler - thrombus in right axillary vein extending into the right subclavian vein.

CTPA was advised by reporting radiologist due to the extent of thrombus. This identified a small sub segmental PE in the right lower lobe.

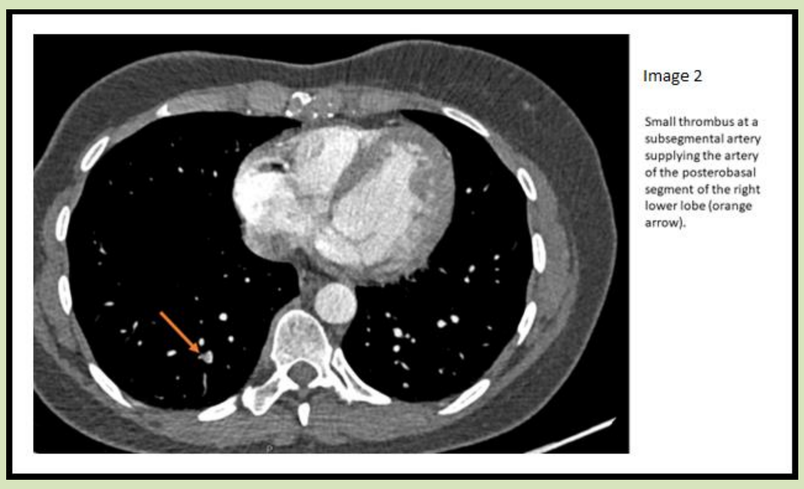


Image 2

Small thrombus at a subsegmental artery supplying the artery of the posterobasal segment of the right lower lobe (orange arrow).

Patient commenced on warfarin therapy with bridging enoxaparin until INR was >2.0

Subsequent investigation excluded any other predisposing condition for development of VTE

3. Case B

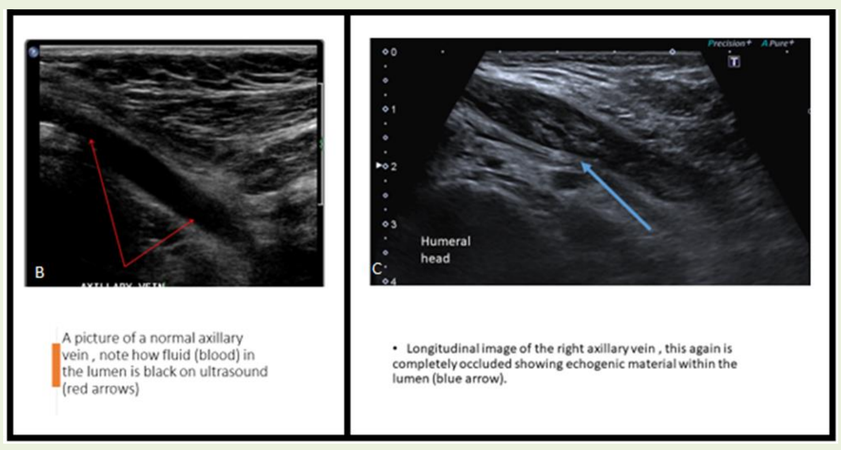
31y/o female; no significant past medical history. Presented with 7 day history of right sided upper arm pain and mild swelling. Symptoms developed after exercise, initially right shoulder/scapular pain before spreading to the upper arm. Examination revealed an area of erythema over upper arm with evidence of venous distension but no overt oedema. Associated tenderness on palpation of the medial aspect of the upper arm and mild reduction in shoulder range of movement.

Constans Criteria score 1

D-Dimer normal.

High clinical suspicion for UEDVT despite scoring tool and D-Dimer result.

Right upper limb US Doppler - confirmed occlusive thrombus in the basilic, axillary and subclavian veins with patent internal jugular vein.



A picture of a normal axillary vein , note how fluid (blood) in the lumen is black on ultrasound (red arrows)

• Longitudinal image of the right axillary vein , this again is completely occluded showing echogenic material within the lumen (blue arrow).

Patient commenced on warfarin therapy with bridging enoxaparin until the INR was >2.0

Subsequent investigation excluded any other predisposing condition for development of VTE

Both cases of upper limb thrombosis likely associated with strenuous exercise (Paget Schroetter Syndrome)

4. Limitations of D-Dimer Assays

The ACLTOP 750 CTS analyser, produced by Werfen, is capable of performing clotting screens, chromogenic and immunological assays.

A number of D-Dimer agents are available. D-dimer reagent used in relation to these clinical cases within the the Northern Trust is HemosIL D-Dimer HS. However, this will change to HemosIL D-Dimer HS 500 due to regional procurement within Northern Ireland. Both these reagents are produced by Werfen, the only difference being the fibrinogen equivalence of the HS 500 reagent leading to different units/reference ranges in reporting.

Within the Belfast Trust, there is occasional use of the STA® Liatest DDI PLUS reagent for the testing of D-Dimer using STAGO Compact Max 3 analyser.

D-Dimers are soluble derivatives produced from degradation of cross linked fibrin clot by plasmin. Both HemosIL D-Dimer HS, and HemosIL D-Dimer HS 500 are latex reagents comprised of polystyrene particles uniformly coated with F(ab')2 fragment from the monoclonal antibody MA-8D3 which is highly specific for D-dimer domains. **The product literature asserts that the use of the F(ab')2 fragment permits more specific identification of D-dimer and avoids interference with endogenous factors such as Rheumatoid factor[5,6].** The STA® DDI PLUS reagent is a similar product, with latex particles covalently bonded to a monoclonal antibody against D-Dimer.[7]

Photometry is used to measure agglutination, and thereby D-Dimer levels for all of the reagents described.

The HemosIL literature states limitations/potential inference factors which should be considered when interpreting D-dimer results.

In the context of ACLTOP analysers being operated with the aforementioned HemosIL reagents;

- providing haemoglobin contamination is <500mg/dL
- bilirubin <18mg/dL, triglycerides <1327mg/dL
- RF < 1400UI/mL
- fibrinogen degradation products (FDPs) <10micrograms/mL

no interference with quantitative detection of D-Dimer ought to occur[5,6].

Additionally, both HemosIL reagents contain a **buffer against Human Anti-murine Antibodies (HAMA)**, the presence of which may lead to over-estimation of D-Dimer levels[5,6]. Patients with HAMA will have previous exposure to mouse derived monoclonal antibodies (*e.g.* Blinatumomab used in refractory ALL). Therefore, if a patient on immunotherapy has a D-Dimer performed which is elevated, due diligence should be undertaken to assess for potential HAMA and ensure appropriate management is given to the patient.

STA® DDI PLUS shows similar limitations while also having a buffer for HAMA. Haemoglobin concentration ought to be < 2g/L, conjugated and unconjugated bilirubin <29mg/dL and 20mg/dL respectively, RF <1000iU/mL and FDPs <15mircograms/mL. Similarly, cloudy plasma may lead to underestimation of D-dimer and significant presence of heparin/heparinoids leads to test insensitivity.[7]

5. Conclusion

- D-Dimer assays are frequently combined with pre-test probability to rule out VTE, availing of their strong negative predictive value. This case series confirms that the high negative predictive value of D-dimer assays in conjunction with the Constans criteria are not 100% reliable and caution ought to be used in utilising it this scoring tool.
- Both these cases allude to the potential for UEDVT to be missed if significant weight is put upon D-Dimer levels in ruling out thrombosis where the Constans score is 1 or less. Such cases will be most commonly encountered by Emergency Medicine and Acute Medical teams.
- Regarding the limitations/potential interference factors described for HemosIL D-Dimer HS, HemosIL D-Dimer HS 500 and STA® Liatest DDI PLUS; in real terms, the levels are to an extreme which is unlikely to be frequently encountered in clinical practice.

  Recommendation: If there is incongruence between clinical presentation of probable VTE and a negative D-Dimer result, then an open mind should be given to potential assay interference. Such clinical scenarios could include, decompensated liver failure, rhabdomyolysis, metabolic states with elevated lipids or acute flare of rheumatological disease with elevated serological markers.
- Incongruent results should prompt discussion with local haematology/coagulation laboratory as to whether potential interference could be causing an inappropriate D-dimer reading. This may identify issues with sample acquisition in the clinical area or in sample preparation at lab level.

References

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