HIT Antiphospholipid Syndrome with Rivaroxaban? Not so fast.

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Introduction

Antiphospholipid syndrome (APS) is an acquired autoimmune condition characterised by venous, arterial and microvascular thromboses in the presence of antiphospholipid antibodies (aPL). The mainstay of APS treatment is lifelong anticoagulation with warfarin, however recently direct oral anticoagulants (DOACs) have been proposed as a potential alternative[1].

Clinical features and Case Timeline

A 53-year-old Caucasian female was diagnosed with triple antibody positive APS in 2015. Due to past difficulties around INR (international normalised ratio) stabilisation and patient preference rivaroxaban 20mg orally daily was initiated at that time instead of warfarin. Other past medical history included chronic lower limb ischemia, depression, pre-diabetes, ex-smoker (10 pack year history) and iron deficiency anaemia.

In 2018 the patient presented to the Emergency Department (ED) with fever, painful dusky lower limbs and necrotic toes diagnosed as acute ischemia secondary to distal embolism. Rivaroxaban was changed initially to therapeutic enoxaparin, then a heparin infusion in preparation for surgery. A below knee amputation (BKA) was performed and enoxaparin was recommenced post operatively. Subsequently heparin induced thrombocytopenia (HIT) was diagnosed and enoxaparin was ceased and switched to fondaparinux. Warfarin was then commenced, however further thrombosis was later noted resulting in an increased INR target range and the addition of aspirin.

Day 1
- ED presentation
- Platelets = 239 x10^9/L
- Doppler ultrasound: Acute on chronic bilateral limb ischemia

Day 2
- Rivaroxaban changed to therapeutic enoxaparin

Day 4
- Commenced on heparin infusion in preparation for surgery
- Bilateral femoral thrombectomies and left leg fasciotomy performed

Day 8
- Left BKA
- Heparin changed to enoxaparin

Day 13
- Platelets dropped to 70x10^9/L
- HIT suspected
- Enoxaparin ceased, fondaparinux commenced

Day 14
- Confirmed diagnosis of HIT
- Warfarin to commence when platelets return to greater than 150x10^9/L and fondaparinux to continue until INR therapeutic

Day 19
- Platelets = 161x10^9/L
- Warfarin commenced with target INR of 2-3

Day 49
- Thrombotic occlusion of left common iliac artery stent found
- Kissing iliac stent extension + aorto-iliac stent placed

Day 50
- Warfarin target range increased to 2.5-3.5
- Aspirin commenced

Day 70
- Nil further thrombosis with improved healing of stump noted

Figure 1: Case Timeline

APS Risk Factors and DOACs

APS is a heterogeneous condition with the risk of thrombotic complications related to the presence of up to three specific antibodies. The presence of all three antibodies known as triple positive APS has shown to be associated with the highest risk of thromboembolic events [5].

Subsequent to this patient's admission, the TRAPS trial was published (2018). This randomised non-inferiority study compared rivaroxaban and warfarin in patients with triple positive APS. The trial was terminated prematurely due to an excess number of thrombotic events in the rivaroxaban arm, leading the author to conclude rivaroxaban being of no benefit in triple positive APS[3]. The incidence of multiple thrombotic complications whilst on rivaroxaban in this particular case further supports the findings of the TRAPS trial.

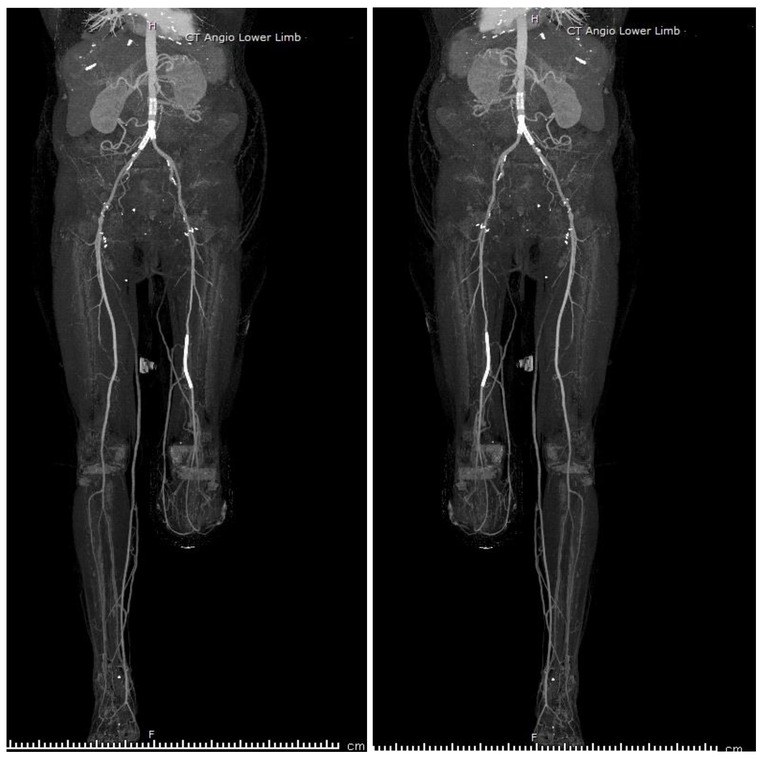

Figure 2: CT Angiography post BKA

APS and HIT

APS and HIT are both antibody-mediated conditions which can result in a hypercoagulable state and thrombocytopenia. Various case reports have noted the coexistence of both conditions in individual patients. It has been proposed that patients with APS may have a higher predisposition to developing HIT[2].

The diagnosis of HIT can be confirmed using immunoassays to detect platelet factor 4 (PF4)-heparin complex IgG antibodies. Patients with APS can test positive for PF4-heparin complex antibodies in the absence of true HIT, leading to false positive results[7]. In this case, a serotonin release assay was also performed with both positive results indicating a true case of HIT[2]. The increasing platelet levels post the cessation of heparin further supported the accurate diagnosis of HIT.

Warfarin and INR

Despite warfarin being the mainstay of treatment, target INR range for the various APS populations is not well established. Systematic reviews have shown that despite receiving anticoagulation, APS patients with arterial events (e.g. critical limb ischemia) have a higher recurrence of events compared to those with venous events[1]. Therefore different treatment targets for various the APS populations has been proposed[6] (Refer to table 1).

APS Features	Proposed INR target range [6]
Non triple positive APS with venous events	2-3
• Triple positive APS • APS with previous arterial events	3-4 OR 2.5-3.5 plus aspirin

Table 1: Proposed treatment recommendations for APS

Despite the patient's previous difficulties maintaining a stable INR, her INR of 2-3 was consistently maintained as an inpatient, however further thrombi were found upon repeat scans. Given the high risk of this patient and the presence of further thrombi the target INR range was increased to 2.5-3.5 and aspirin was added.

A systematic review shows that INR > 3 appears to be correlated with a lower risk of thrombosis in high-risk APS patients[1]. The use of aspirin in the APS is recommended by some experts, but its efficacy has not been well established [6].

Given the patient's history of troubles maintaining a steady INR whilst on warfarin, a point of care (POC) device was suggested for the patient to monitor her INR. The use of POC INR testing in patients with triple positive APS however is not currently recommended due to concerns regarding the accuracy of readings[4].

An INR POC device

Conclusion

Rivaroxaban has been proposed as an alternative long-term anticoagulation option for patients with APS as it has less burdensome monitoring requirements than warfarin. However, this case adds to the concerns regarding its lack of efficacy in APS, especially for high-risk cases with triple positive aPL profiles and arterial thrombosis. This case also describes a rare concurrent, and potentially catastrophic, presentation of HIT in APS, and highlights the importance of closely monitoring for it in this population.

References

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