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CASE REPORT

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Case of severe thrombocytopenia with recurrent extensive deep vein thrombosis due to antiphospholipid syndrome, management challenge

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Key Clinical Message

Severe thrombocytopenia in secondary antiphospholipid syndrome (APS) presents a significant management challenge. This case highlights the complexity of managing APS-related thrombocytopenia, requiring a nuanced approach to balancing bleeding and thrombotic risks. Intravenous immunoglobulin, followed by a short course of steroids, successfully increased platelet counts without adverse bleeding or thrombotic events. Initiating therapeutic anticoagulation with Warfarin was delayed until platelet counts exceeded 50×10^3/μL, emphasizing the cautious approach required in such cases to mitigate thrombotic risks while avoiding bleeding complications.

KEYWORDS

anticoagulation, antiphospholipid syndrome, APS, deep vein thrombosis, DVT, thrombocytopenia

1 | INTRODUCTION

Antiphospholipid syndrome (APS) is a systemic autoimmune condition marked by thrombosis in both veins and arteries, recurrent miscarriages, and consistently high levels of antiphospholipid (aPL) antibodies like lupus anticoagulant (LAC), anti-β2-glycoprotein I (anti-β2GPI), and anticardiolipin (aCL) antibodies. This syndrome can manifest independently (primary APS [PAPS]) or alongside other autoimmune disorders (secondary APS [SAPS]). A small fraction (<1%) of APS cases experience a severe form known as catastrophic antiphospholipid syndrome (CAPS), characterized by widespread organ clotting occurring rapidly.[1]

The prevalence of thrombocytopenia in antiphospholipid syndrome (APS) varies significantly, ranging from 16% to 53%. It tends to be more common in secondary APS compared to primary APS, with the rates for secondary APS being approximately double those for primary APS.[2] Recent studies suggest that thrombocytopenia might indicate a higher risk of other complications in APS. Specifically, a study using the aGAPSS risk score showed that 21% of patients with thrombocytopenia had a higher score than those without additional criteria

manifestations, indicating that thrombocytopenia could be a marker for increased APS-related complications.[3]

2 | CASE HISTORY/ EXAMINATION

We are presenting a 35-year-old male with a history of recurrent unprovoked deep vein thrombosis (DVT) of the left lower limb. The patient had two episodes of left lower limb thrombosis in 2017, for which he was admitted, treated, and discharged with rivaroxaban 15 mg. Readmitted in 2018 with the same complaint and found to have thrombocytopenia (48 × 10^3/μL), so rivaroxaban stopped, and the patient was shifted to warfarin, with a referral to a hematology clinic for further workup. The patient was seen by the hematologist, whose diagnosis was pseudo-thrombocytopenia due to platelet clumps; however, AntidsDNA Ab and ANA CTD were positive. On this admission, the patient presented to the emergency department complaining of a 3-day history of painful left leg swelling, redness, and ulceration with oozing of blood. He had no fever, cough, chest pain, hemoptysis, or right leg symptoms. On examination, left leg swelling, redness, warmth, with medial ulcer measuring 2 × 3 cm. Posterior tibial and dorsalis pedis pulses were palpable. The rest of the examination was normal.

3 | INVESTIGATIONS AND TREATMENT

Laboratory investigations showed low hemoglobin of 10.2 g/dL, platelet estimation of 24 × 10^3/μL, and normal liver and kidney function tests. The coagulation profile showed prothrombin time of 13.6 s, INR 1.2, and a prolonged activated partial thromboplastin time (APTT) of 82.8 s.

Doppler venous Ultrasound of left lower limb showed extensive left lower limb DVT with occluded and non-compressible left CFV, SFV, popliteal vein, and PTV by an isoechoic intra-luminal thrombus. The patient was admitted to the High Dependency Unit (HDU) and started on heparin infusion 25,000 units and Clindamycin 150 mg for cellulitis. Further workup was sent (Table 1), which showed normal protein C and protein S activity. Autoimmune work up revealed positive Anti-ds DNA antibodies, lupus anticoagulants, anti-cardiolipin AB, anti-B2 glycoprotein IgG, and IgM. So, the diagnosis of secondary APS was finalized; however, the patient did not show any signs or symptoms of systemic lupus erythematosus (SLE) or any other connective tissue disease prior to or during admission.

TABLE 1 Auto immune work up.

Lab test	Result	Interpretation
Rheumatoid factor	<10 IU/mL	Normal
Anti CCP Ab	<8 U/mL	Normal
Anti-nuclear Ab	Negative	
Anti dsDNA Ab	69.00 IU/mL	Positive
ANCA	Negative	
Anti myeloperoxidase Ab	0.20 IU/mL	Negative
Anti proteinase 3 Ab	0.70 IU/mL	Negative
Lupus anticoagulant	Positive	Repeat after 12 weeks as the patient was on heparin.
Anti cardiolipin Ab IgG	>418.00 GPL	Positive
Anti cardiolipin Ab IgM	12.00 MPL	Weak Positive
Anti B2 glycoprotein IgG	197.00 U/mL	Positive
Anti B2 glycoprotein IgM	53.00 U/mL	Positive
ANA CTD Int	Positive	
C3	1.24 gm/L	Normal
C4	0.14 gm/L	Normal
Protein C activity	93.3%	Normal
Protein S activity	87.2%	Normal

On the second day of admission, the patient's platelet count decreased to 9 × 10^3/μL, so a heparin infusion was held, platelets were sent in a citrate bottle for more accurate results, and an HIT test was done (<0.7 U/mL). Platelet citrate count reported as 9 × 10^3/μL so IVIG started after discussing with the hematologist.

On the third day of admission, platelet count improved to 22 × 10^3/μL. The patient monitored closely for any symptoms or signs of bleeding or pulmonary embolism (PE).

On the fourth day of admission, the patient had completed 48 hours of IVIG, so it was stopped and IV dexamethasone 40 mg started; platelet count was 38 × 10^3/μL. The decision was made by the hematologist that once platelet count is more than 50 × 10^3/μL to start therapeutic anticoagulation. The next day platelet count was 48 × 10^3/μL.

On Day 6 of admission, the platelet count reached 85 × 10^3/μL, INR 1.2. So, warfarin 7 mg was cautiously started, and INR followed closely.

The following 3 days, the patient continued to receive warfarin, and the dose was titrated according to INR with an INR target of 2–3.

4 | CONCLUSION AND RESULTS

The patient was discharged after 9 days in hospital stable, with a platelet count of 146 × 10^3/μL, and a lifelong

anticoagulation, hydroxychloroquine, and tapering of steroids to be followed at hematology, vascular, rheumatology, and anticoagulation clinics.

5 | DISCUSSION

While thrombotic and obstetric complications are the sole clinical events outlined in the APS classification criteria, numerous additional manifestations, such as nephropathy, cardiac valve lesions, neurological issues, skin problems, and cytopenia's, are commonly observed in APS. Among these, thrombocytopenia appears to be the most frequent, with certain APS cohorts showing a higher prevalence of thrombocytopenia compared to obstetric complications. Due to its notable prevalence, some initial efforts to define APS included thrombocytopenia as a clinical event warranting APS classification.[4] Despite thrombocytopenia's high prevalence in APS, much remains to be understood regarding its underlying causes, prognostic significance, and management strategies.

Estimates regarding the prevalence of thrombocytopenia in APS vary widely, ranging from 16% to 53%.[3] higher occurrence of thrombocytopenia in secondary APS compared to primary APS, with rates roughly doubling. For example, a recent analysis of a large international cohort found thrombocytopenia in 28% of patients with secondary APS and 16% with primary APS.[3] Which was the case in our patient, who has secondary APS with a very low platelet count.

Recent literature increasingly suggests that thrombocytopenia may serve as a predictor of other complications in APS, such as Radin et al.[2] recently utilized a validated APS risk score (aGAPSS) in a group of primary APS patients, including those with extra-criteria manifestations like thrombocytopenia. They found that 21% of patients with thrombocytopenia had a higher aGAPSS score compared to those without extra criteria manifestations (10.6 vs. 8.2).[3] In this case, the patient experienced one episode of non-sustaining ventricular tachycardia (NSVT), which might be a complication related to APS and severe thrombocytopenia.

In the management of antiphospholipid syndrome (APS), traditional therapy involves vitamin K antagonists (Warfarin) with an INR target of 2–3, often with initial concurrent use of low molecular weight heparin (LMWH) or unfractionated heparin (UFH). Despite the emergence of direct oral anticoagulants (DOACs), their application in APS is limited due to concerns about increased risk of thrombosis, particularly in high-risk patients. While some studies suggest similar effectiveness between DOACs and VKAs, others indicate a higher-than-expected risk of thrombosis associated with DOACs in certain subsets of APS patients. Large-scale trials like TRAPS have demonstrated significantly more thrombotic events with rivaroxaban compared to warfarin in triple-positive APS patients, resulting in early termination of the trial.[5] These concerns are experienced in our case, who initially received rivaroxaban and consequently developed 2 episodes of deep vein thrombosis (DVT) while on rivaroxaban.

Currently, there are no established guidelines or conclusive evidence regarding the treatment of thrombocytopenia in APS. APS patients with moderate thrombocytopenia have been observed to have a thrombosis risk of 40%, whereas those with severe thrombocytopenia show a reduced risk of thrombosis at 9%. Consequently, even in the presence of thrombocytopenia, there remains a strong imperative for anticoagulation therapy.[6] In most instances, thrombocytopenia in APS is mild to moderate, with platelet counts exceeding 50×10^{9}/L. Generally, it is believed that thrombocytopenia in such cases does not necessitate specific treatment.[3,7] Unfortunately, this was not the case in our patient, who had severe thrombocytopenia with platelet count of 24×10^{3}/μL followed the second day by a platelet count of 9×10^{3}/μL.

Although the literature addresses the treatment of catastrophic APS (CAPS), which is a form of APS characterized by severe thrombocytopenia and thrombotic microangiopathy leading to failure of multiple organs, affecting three or more organs typically.[7] Treatment for catastrophic APS typically involves a combination of anticoagulation, corticosteroids, intravenous immunoglobulins, plasma exchange, and other therapeutic measures.[8] There are no clear guidelines to treat APS with severe thrombocytopenia and without CAPS.

In this challenging scenario, treatment recommendations rely on expert opinions or extrapolations from cancer literature. Both bleeding and thrombotic risks must be carefully considered before initiating anticoagulation therapy. Shared decision-making is crucial in all cases, with treatment tailored to everyone. Typically, many experts suggest that full anticoagulation can be safely administered when platelet counts exceed 50,000/mL. However, due to the exclusion of patients with platelet counts below 50,000/mL in controlled anticoagulant studies, there is limited prospective evidence to inform specific recommendations.[3] Our approach to this patient, who has a platelet count of 24×10^{3}/μL anticoagulation with heparin was stopped immediately after the platelet count dropped to 9×10^{3}/μL, risks and benefits weighted, and a multidisciplinary decision to start intravenous immunoglobulin (IVIG) followed by a short course (4 days) of steroids was taken. Which improved the platelet count without any bleeding or thrombotic complications encountered. Once platelet count had reached more than 50×10^{3}/μL, anticoagulation (Warfarin) started with INR target of 2–3.

AUTHOR CONTRIBUTIONS

Bassem Al Hariri: Supervision; validation; writing – original draft; writing – review and editing. **Gaydaa Ali Ahmed Ali:** Validation; writing – original draft; writing – review and editing. **Arwa Elfatih Mohamed Ali:** Writing – review and editing. **Mohamed Elfatih MohamedAli:** Writing – review and editing. **Feroz Jenner Poolakundan:** Writing – review and editing. **Muhammad Sharif:** Writing – review and editing. **Memon Noor Illahi:** Supervision; writing – review and editing.

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The authors have declared that no competing interests exist.

DISCLOSURE

The authors solemnly declare that they have no financial disclosures. This manuscript has not been published nor is under consideration for publication elsewhere. All co-authors have agreed to the submission of this publication.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

CONSENT

Written informed consent was obtained from the patient to publish this case report and any accompanying images.

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