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CORRESPONDENCE

Recurrent Arterial and Venous Thrombosis in Chronic Immune Thrombocytopenia: Clinical Paradox and Therapeutic Challenges

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Dear Editor,

Immune thrombocytopenia (ITP) is characterized by humoral and cellular autoimmunity-mediated thrombocytopenia ($< 100 \times 10^9$/l). Although clinical history is marked by bleeding, an increased thrombotic tendency has been recently recognised in ITP [1]. While thromboembolic events (TEE) have been described in ITP, no case of recurrent arterial thrombosis (AT) and venous thromboembolism (VTE) in the same patient has been reported.

A 40-year-old lady presented to the surgical emergency in September 2018 with pain and swelling of the right upper limb (RUL). On examination, right brachial and radial pulses were not palpable. RUL was diffusely swollen and tender, overlying skin was shiny, and local exam revealed blackish discoloration of the digits. Her vitals, and rest of the systemic examination was normal. Doppler ultrasound showed thrombosis of the right brachial and axillary veins, and distal brachial, radial, and ulnar arteries. Blood investigations were: hemoglobin: 120 g/l, white cell count—9.2×10^9/l, and platelets—20×10^9/l. Peripheral smear showed large platelets, and no evidence of schistocytes. Serum biochemistry including lactate dehydrogenase was normal. She underwent an emergency above elbow amputation of the RUL after platelet transfusion, and was advised oral warfarin after an initial overlap with subcutaneous enoxaparin (1 mg/kg/day). She was compliant with warfarin (INR: 2–3), and had no bleeding symptoms. In November 2018, she presented to neurology emergency with sudden onset numbness and weakness of the left UL. Non-contrast CT scan of head revealed an acute right basal ganglia infarct. Warfarin was continued, and oral aspirin and atorvastatin were added. 2D-Echocardiogram, and bilateral carotid doppler were unremarkable. Blood counts showed low platelets ($20–30 \times 10^9$/l). She was referred to hematology clinic for the evaluation of thrombocytopenia. Her past medical history was significant for persistent thrombocytopenia ($< 30 \times 10^9$/l) since past 8 years, and 2 episodes of lower limb deep vein thrombosis (DVT) in between. History was negative for diabetes, hypertension, and smoking. She was regularly taking warfarin since her first DVT episode, but discontinued it only recently. Her HIV and Hepatitis-C serology, Australia antigen, anti-nuclear antibody, C^{14} urea breath test for Helicobacter pylori, and direct anti-globulin test were negative, and thyroid function test was normal. Her antiphospholipid antibody, Leiden Factor V mutation, and anti-neutrophil cytoplasmic antibody were negative, coagulation screen, serum homocysteine, Factor VIII activity, fibrinogen, and von Willebrand factor (vWF) antigen were normal, and paroxysmal nocturnal hemoglobinuria clone (PNH) was undetectable. Treatment with oral prednisolone (1 mg/kg/day) resulted in normalization of platelet count within 2-weeks. During steroid tapering, she had recurrent thrombocytopenia, and required low-dose (20 mg) of prednisolone to maintain a platelet count $> 50 \times 10^9$/l. Based on exclusion of other causes of thrombocytopenia, and therapeutic response to steroids, a diagnosis of chronic primary ITP was established. Patient is presently on a combination of warfarin, aspirin, and low-dose prednisolone. She is planned for an indefinite anti-coagulation.

A meta-analysis of five large population-based studies established that there is a two-fold increased risk of VTE, and a trend towards increased risk of AT in ITP as compared to the general population [2]. In addition to the host

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and treatment-related factors, ITP per-se is a thrombophilic state, largely attributable to younger platelets with a greater thrombogenic potential. Platelet micro-particles (PMP) produced during immune-mediated platelet destruction are pro-thrombotic, and contribute to the TEE in ITP. Possible mechanisms underlying the TEE in ITP have been summarized in Table 1 [3–7]. Certain questions from the index case needs discussion. (1) Recognition of thrombocytopenia in a case of thrombosis is essential. Since this combination could be a manifestation of a number of disorders including, but not limited to PNH, thrombotic thrombocytopenic purpura (TTP), anti-phospholipid antibody syndrome (APS), and disseminated intravascular coagulation (DIC), a thorough history, diligent clinical examination, careful peripheral blood smear review, and exclusion of potential secondary causes of thrombocytopenia are needed to establish a working clinical diagnosis of primary ITP. This distinction is relevant from both diagnostic, therapeutic, and research perspective. A diagnosis of primary ITP could provide both patients and physicians, a plausible explanation for the thrombotic event, in a so-called 'idiopathic' thrombosis. (2) Index case tolerated amputation procedure quiet well, and had no bleeding symptoms while taking warfarin, despite severe thrombocytopenia (20–30 $\times$ 10^9/l). The concept of 'Rebalanced hemostasis' described initially in liver disorders has been extended to ITP. Kim et al. demonstrated that vWF antigen level was elevated in about 40% of ITP cases. Patients with elevated vWF had better thromboelastography (TEG) profile, and less frequent bleeding episodes as compared to those with normal vWF level, despite a similar median platelet count in both the groups. They postulated that hemostasis is rebalanced in ITP such that anti-thrombotic phenotype is balanced by the pro-thrombotic mechanisms, providing a plausible explanation for the variable bleeding severity seen in ITP patients at a similar platelet level [7]. This hypothesis strengthens the idea that platelet count is not the sole determinant of bleeding in ITP, and that estimation of the true hemostatic potential of an ITP patient needs an individualised approach taking into consideration a global hemostatic assessment by TEG to predict bleeding, and possibly thrombotic risk, though the latter needs to be validated [8]. (3) Management of thrombosis in the setting of thrombocytopenia is challenging. No formal evidence-based guidance exists, and treatment decisions are generally individualised based on physician's assessment of risk-vs-benefit ratio. This is highlighted in a recent case-based survey of the expert hematologists and general hemato-oncologists, regarding the management of anti-platelet (AP) and anti-coagulant (AC) therapy in ITP. Platelet thresholds for AP/AC were variable (10–100 $\times$ 10^9/l) across the physicians, though a range of 30–50 $\times$ 10^9/l was generally suggested [1]. (4) The choice of therapy deserves a mention. Since PMP are potentially thrombogenic, suppression of PMP production must be the goal of any treatment strategy. This could be achieved by (a) immunosuppressive drugs like corticosteroids/IVIG which block platelet destruction, and consequent PMP production, or (b) calcium-channel blockers like amlodipine, which inhibit the calcium-dependent PMP release [5]. To this

Table 1 Review of the proposed mechanisms contributing to thrombosis in ITP [3–7]

Host factors	1. Age, co-morbidities (diabetes, hypertension, dyslipidaemia), infection
Disease factors	1. Younger, and thrombotically active platelets
	2. Increased PMP produced during immune-mediated platelet destruction. PMP are potentially thrombogenic due to high surface expression of PS, and high content of large multimer of vWF
	3. High prevalence (8.6–73%) of anti-phospholipid antibodies in ITP
	4. Endothelial dysfunction by autoantibodies
	5. Complement activation
	6. Increased circulating platelet-leucocyte-monocyte aggregates
	7. Abnormal pro-coagulant profile at baseline: high vWF, Factor VIII activity, low protein-S, high D-dimers
	8. Reduced nitric oxide
	9. Low ADAMTS-13 activity
	10. Better TEG profile (in those with high vWF): shorter CFT, and larger α-angle
Treatment factors	1. IVIG: increases serum viscosity, induces vasospasm, and causes platelet activation
	2. Corticosteroids: increased hypercoagulable state
	3. Danazol: implicated in arterial thrombosis in ITP
	4. Thrombopoietin-receptor agonists (Eltrombopag and Romiplostim)
	5. Splenectomy: increased risk post-splenectomy, highest within first 90 days

CFT clot formation times; *IVIG* intravenous immunoglobulin; *ITP* immune thrombocytopenia; *PMP* platelet micro-particles; *PS* phosphatidylserine; *TEG* thromboelastography; *vWF* von Willebrand factor

backbone, AP/AC are added. It is noteworthy that, AP drugs (aspirin, dipyridamole) do not have any significant effect on PMP [9]. However, in the index case, we chose to combine aspirin and warfarin due to recurrent AT and VTE. (5) Risk of recurrent thrombosis, and the duration of AC therapy in ITP are clinically relevant questions. This has been addressed in a recent follow-up study of 49 ITP cases. Twenty seven percent patients with VTE and ITP had a recurrent VTE after a median delay of 110 months (range, 8–401 months), and median thrombosis-free survival was 8.8 months [10]. This study, and index case suggests that long-term (or indefinite) anti-coagulation is reasonable in ITP patients, especially those who have an unprovoked VTE, or recurrent VTE. Concurrent treatment of ITP with corticosteroids, at a dose enough to maintain a 'safe' platelet count ($> 30–50 \times 10^9$/l) may enable a smooth AC therapy, without an increased bleeding risk.

We conclude that although bleeding remains the dominant clinical manifestation, a potential thrombogenic risk associated with ITP must be recognised. Individualised treatment algorithms based on comprehensive assessment of pro-and anti-thrombotic factors in a particular case is essential. Although global assay of hemostasis may have some utility in predicting the bleeding risk in ITP, models which enable risk-stratification of the thrombotic risk are desirable. Treatment with immunosuppressive therapy is safe, and should be the backbone of therapy in ITP with thrombosis, in order to a safely deliver antithrombotic therapy. Considering a significant risk of recurrence, an option of indefinite anticoagulation may be explored, and discussed with the patient.

Compliance with Ethical Standards

Conflict of interest Authors have no conflicts of interests to declare.

Ethical Standards The article has not been submitted elsewhere for consideration of publication. The article complies with the ethical standards by declaration of Helsinki.

Informed Consent The authors state that a written and informed consent was obtained from the patient prior to publication.

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