Management of Recurrent Venous Thromboembolism in Severe Immune Thrombocytopenia: A Case Report and a Review of the Literature

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Abstract

We report a case of a 58-year-old man with recurrent unprovoked deep vein thrombosis (DVT) and severe immune thrombocytopenia (ITP) with a platelet count of 19×10^9/L. We further review studies reporting venous thromboembolism (VTE) in patients with severe ITP ($\leq 35 \times 10^9$/L) and identified 14 patients highlighting VTE risk factors and management of these patients. The present case had several risk factors for VTE (previous DVT, obesity, heterozygosity for factor V Leiden mutation, and previous splenectomy). The patient was initially treated with low-molecular-weight heparin followed by long-term apixaban treatment. The literature review together with our case demonstrates that VTE in severe ITP ($\leq 35 \times 10^9$/L) can occur in patients with VTE risk factors and antithrombotic management of these patients can be achieved without bleeding depending on severity of thrombocytopenia either by full or reduced dose of anticoagulation together with ITP therapy.

Keywords

- immune thrombocytopenia
- venous thromboembolism
- thrombotic disorder

Introduction

Immune thrombocytopenia (ITP) is a rare autoimmune disease characterized by autoantibody-mediated destruction and suboptimal bone-marrow production of platelets and associated with increased risk of bleeding especially with persistently low platelet counts of $<30 \times 10^9$/L.[1]

Notably, ITP has increasingly been recognized as a thrombotic disorder with observed higher rates of thrombosis in ITP patients than non-ITP patients.[2,3] However, antithrombotic management poses a clinical challenge in severe ITP patients with thrombosis because of bleeding risk.[4] No high-quality evidence exists to guide the management of anticoagulation (AC) therapy in patients with ITP. Here, we describe a case of recurrent unprovoked deep vein thrombosis (DVT) in a patient with ITP and a platelet count of $<19 \times 109$/L and further discuss risk factors as well as treatment options for venous thromboembolism (VTE). The case is accompanied by a literature review focusing on risk factors and the antithrombotic management of patients with VTE and severe ITP ($\leq 35 \times 10^9$/L).

Case Presentation

A 58-year-old man, who is obese (body mass index: 35), was referred to the emergency department (ED) under suspicion of DVT due to pain, swelling, and red discoloration of his lower right leg. At the time of admission, the patient was hemodynamically stabile. The medical records of the patient revealed ITP and a previous DVT. The patient had been diagnosed with primary ITP in 2011 based on the platelet

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count $<100 \times 10^9$/L with the exclusion of other causes of thrombocytopenia. Blood smear and bone marrow investigation showed normal morphology of thrombocytes. The initial treatment was unsuccessful with high doses of corticosteroids (Cs) and was likewise unsatisfactory despite the addition of rituximab. Good clinical response was achieved after the patient underwent splenectomy. The patient suffered from epistaxis, gum bleeding, and tendency to superficial bleeding from the skin prior to splenectomy.

One year before the current admission to the ED, the patient had been diagnosed with an unprovoked DVT of the right v. poplitea while he had thrombocytopenia (30×10^9/L). A thrombophilia screening showed that the patient was heterozygote for factor V Leiden (FVL) mutation and had high plasminogen activator inhibitor-1 (PAI-1) and a slightly low antithrombin level of 77% (►**Table 1**). No other autoimmune diseases, including antiphospholipid syndrome (APS), had been discovered during this assessment. The patient was also investigated for JAK2 mutation and found to be negative for this mutation. The patient was treated with 10,000 IE of low-molecular-weight heparin (LMWH) for 6 months.

Clinical presentation of the patient at the current admission included a Wells score of 2 and high D-dimer measurement, suggesting a possible new unprovoked DVT. Consequently, ultrasonography of the lower extremity confirmed the diagnosis by revealing thrombosis of v. femoralis superficialis and v. poplitea in the right extremity, requiring AC treatment. Blood sampling at admission also revealed severe thrombocytopenia (19×10^9/L) indicating a risk of bleeding—a risk that would be exacerbated if AC treatment was initiated. Thus, to address the risk of bleeding, two units of thrombocyte transfusions were given to increase the thrombocyte count to above 50×10^9/L and thereafter 18,000 IE of LMWH was administered. Initial LMWH was monitored by anti-Xa measurement and later reduced to 10,000 IE daily for the following 14 days. The patient's VTE bleed score was calculated to be low (1.5 point) at the time of the DVT diagnosis.[5] After acute treatment, thrombopoietin receptor agonist (TPO-ra) was administered to address the persistent thrombocytopenia. LMWH was afterward changed to apixaban 5 mg × 2 for 6 months and later reduced to 2.5 mg × 2 daily. The patient was planned to continue long-term treatment with reduced dose of apixaban together with TPO-ra following VTE conference consensus and dialogue with the patient. At following controls, the thrombocyte count was normalized and the patient reported no signs of renewed thrombosis or bleeding under apixaban treatment except mild rectal bleeding. To address the rectal bleeding, the patient had a colonoscopy where an inflamed mucous membrane was found. Thereafter the patient was referred to the department of gastroenterology for further investigation for the inflammatory bowel disease.

Table 1 The results of the thrombophilia investigation of the patient after the first incident of DVT

Coagulation tests	Results of the patient	Reference intervals
APTT (s)	24	22–28
INR	0.96	<1.20
Thrombin time (s)	19	<20
Antithrombin (IIa, 10^3 IU/L)	0.77	0.80–1.20
Antithrombin (Xa 10^3 IU/L)	0.77	0.80–1.20
Antithrombin (imm. g/L)	0.20	0.19–0.31
Protein S frit (imm.)	1.12	0.74–1.46
Protein C (enz.)	1.10	0.70–1.40
Factor VIII	1.28	0.50–1.50
Fibrin D-dimer (mg/L(FEU))	0.84	<0.60
Plasminogen activator inhibitor-1 (µg/L)	158.8	8.6–45.9
Fibrinogen (µmol/L)	7.8	5.2–12.6
Factor V Leiden	Heterozygote	-
Factor II (prothrombin)	Negative	-
Lupus anticoagulant	Negative	-
Cardiolipin IgG (GPL-U/mL)	3	<21
Cardiolipin IgM (MPL-U/mL)	1	<41
Beta-2-glycoprotein IgG (AU/mL)	1	<11
Beta-2-glycoprotein IgM (AU/mL)	<3	<13
CRP (mg/L)	3.3	<6.0

Abbreviations: APTT; activated partial thromboplastin time, CRP; C-reactive protein, DVT; deep vein thrombosis, FEU; fibrinogen equivalent units, GPL, IgG fosfolipid, INR; international normalized ratio, MPL; IgM fosfolipid.

Discussion

In this article, we report a case with recurrent unprovoked DVT and severe ITP together with a literature review of studies including case series, reports, and observational studies reporting VTE in patients with ITP, identified in PubMed, through July 2022. The literature search was further supplemented by a manual review of the reference lists in identified publications. Only studies reporting management of VTE in patient with ITP having platelet a count $\leq 35 \times 10^9$/L at the time of the VTE diagnosis were included.

Our patient presented with platelet counts $<19 \times 10^9$/L, and he still developed DVT indicating that severe thrombocytopenia does not exclude the possibility of thrombotic events. This notion is also supported by our literature review, where 14 cases were identified. The data of all 15 patients including our case are presented in ►Table 2.[1,6–13] The underlying pathogenesis behind this prothrombotic tendency in patients with ITP is unclear.[14] Several different possible causes have been suggested including hyperactive immature platelets,[15] platelet microparticles,[14] and dysfunction in complement activation.[16] Furthermore, the risk of VTE in patients with primary ITP may also be increased by splenectomy and treatment with TPO-ra or IG.[6,7,17]

The patient in our case presented with several commonly known risk factors, including a previous DVT,[1] obesity, and a history of splenectomy.[18] Risk factors for thrombosis in ITP was discussed in an excellent review by Swan et al.[19] VTE risk factors were also seen in 12 patients with severe ITP (►Table 2). Our patient has also inherited thrombophilia in the form of heterozygote FVL, which is known to increase the risk of thrombotic event by two to five times compared with the background population.[20] While other thrombophilic conditions such as APS are commonly associated with both ITP and thrombotic events,[17] only very few cases of ITP patients are complicated by FVL.[1,8] Thrombophilia investigation of our case also showed an increased level of PAI-1, which can be presumed to be related to his obesity. Furthermore, the patient had slightly low antithrombin activity (77%) and normal antigen level, which is unlikely to have clinical significance.

Currently, no clear clinical guidelines exist for managing thrombosis in patients with severe ITP. The AC treatment of thrombocytopenic patients is mostly an issue in cancer-associated thrombosis (CAT) and full-dose LMWH for platelet counts $\geq 50 \times 10^9$ /L, and half-dose LMWH for platelets 30 to 50×10^9/L are recommended. In patients with platelets $< 30 \times 10^9$/L, insertion of an inferior vena cava (IVC) filter with prophylactic LMWH and platelet transfusions are suggested.[9,21] For the AC treatment of VTE in severe ITP, expert opinions had inspirations from the recommendations for CAT and a similar threshold of 30×10^9/L has been proposed. However, this is not based on clinical studies. Therefore, in the present study, we have reviewed literature reporting VTE in patients with severe ITP and a platelet count $\leq 35 \times 10^9$/L revealing 14 patients, including 6 patients (patients 1–6; ►Table 2) from the largest series of VTE and its management in ITP reported by Guenno et al. All 15 cases, except 2, received AC treatment. As an initial AC treatment, both LMWH and unfractionated heparin (UIH) were used. Six patients received long-term AC treatment with vitamin K antagonist (VKA; ►Table 2).

No recommendations exist concerning the use of direct oral anticoagulants (DOACs) in severe ITP patients with VTE. Only one study, Kang et al,[10] reported 3-month DOAC treatment in a patient with severe ITP (►Table 2) having DVT and PE. However, despite dabigatran treatment, recurrent PE occurred and this was later changed to rivaroxaban. In the present case, after the acute course, the persistent thrombocytopenia was corrected by TPO-ra and LMWH was changed to apixaban. We consider that long-term treatment with reduced dose of apixaban as a secondary prophylaxis is more convenient than VKA, because of reduced bleeding risk. The patient did not have bleeding tendency except mild rectal bleeding after he had started the long-term AC treatment with low doses of apixaban. However, the safety and efficacy of DOAC have not been systematically assessed in patients with ITP.

One can discuss whether long-term AC treatment for our patient could have been considered after the first DVT because of unprovoked proximal DVT and three risk factors including obesity, a history of splenectomy, and heterozygosity for FVL mutation. The decision concerning the duration of AC depends on the presence of risk factors for VTE recurrence. Heterozygosity for FVL is known not to induce VTE recurrence. Le Guenno et al[1] reported 27% of patients with ITP and VTE ($n = 49$) had VTE recurrence, and the risk of recurrence was increased only in patients with unprovoked VTE before ITP diagnosis or active cancer. Interestingly, in our review, eight patients with severe ITP received long-term AC treatment mostly due to previous VTE or APS (►Table 2).

Notably, no hemorrhagic events were recorded in any of the patients receiving AC treatment including the six patients with persistent platelet count $<35 \times 10^9$/L (►Table 2). However, bleeding is still the most feared complication for patients with ITP. Supporting this, Adelborg et al showed that among patients with chronic ITP, the 1-year risk of cardiovascular events was up to 2%, while 8% experienced a bleeding event within 1 year.[22] In an attempt to address the issue of concurrent risk of bleeding and thrombosis, Balitsky et al[23] suggested a new risk assessment score to predict the net risk of both thrombosis and bleeding in ITP patients requiring AC therapy. This risk score includes two thrombosis-associated risk factors; high thrombotic risk situations (+1 point), recent ITP treatment (+1 point), and two bleeding risk factors; platelets $<20 \times 10^9$/L (−1 point), major bleeding at the time of review (−1 point). A score of 0 or positive score suggests excess thrombotic risk, while negative score suggests excess bleeding risk. The patient in our case would score 0 points (receiving +1 point for recurrent VTE and −1 point for the platelet count of 19×10^9/L) suggesting a trend toward a higher thrombosis risk.

Despite the seemingly increased risk of thrombosis, most reports suggest initial treatment of thrombocytopenia to an acceptable platelet count of $> 50 \times 10^9$/L before initiating standard AC therapy.[9,21] There are different suggested therapeutic

Table 2 Overview of existing literature describing patients with ITP presenting with VTE and a platelet count $\leq 35 \times 10^9$/L

	Age (y) and sex	Type of VTE	Risk factors[a] inducing VTE	Platelet count at VTE (10^9/L)	ITP therapy at or within 1 mo of VTE	Thrombocytopenia treatment	AC treatment at VTE	AC despite platelet count of $\leq 35 \times 10^9$/L	AC treatment duration	Vena cava filter	Bleeding after AC treatment	Ref.
Patient 1	83, M	PE	Cancer	29	No	Cs + IVIG	UIH, LMWH[b]	Unknown	Long term	No	No	1
Patient 2	31, F	ST	aPL	14	Yes, unspecified	IVIG, romiplostim, RIX	LMWH,[b] VKA	Yes	Unknown	No	No	1
Patient 3	83, M	PE, DVT	Unknown	32	No	IVIG	LMWH,[b] VKA	Unknown	Long term	No	No	1
Patient 4	66, F	DVT	Obesity, prev. PE	20	Yes, unspecified	Yes, unspecified	LMWH,[b] VKA	Yes	Long term	No	No	1
Patient 5	71, M	DVT, PE	Unknown	8	No	Unknown	UIH, VKA	Unknown	Unknown	No	No	1
Patient 6	75, M	DVT	aPL, prev. VTEs	29	No	Unknown	LMWH,[b] VKA	Unknown	Long term	No	No	1
Patient 7	80, M	PE	Surgery, low AT	22	No	No	None	No	–	No	–	11
Patient 8	56, F	DVT, PE	IVIG[c]	14	IVIG	Cs, spl	LMWH,[b] VKA	Yes	Unknown	No	No	6
Patient 9	76, F	CVST	Prev. PE	29	Cs	Cs	LMWH,[b] VKA	Yes	Long term	No	No	12
Patient 10	51, F	DVT, PE	Spl	5	Cs	Platelet infusion, Cs	UIH, VKA	No	Unknown	Yes	No	9
Patient 11	59, M	DVT	IVIG,[c] Spl, FVL, VCL	18	Cs, IVIG	IVIG	VKA	Unknown	Long term	No	No	8
Patient 12	1.5, U	PVT	UVC	33	IVIG	No	None	No	–	No	–	13
Patient 13	45, F	CVST	Spl, aPL Romiplostim[c]	35	Romiplostim	No	UIH, VKA	Yes	Long term	No	No	7
Patient 14	54, M	DVT, PE	None	33	No	Cs, IVIG	UIH, dabigatran, LMWH rivaroxaban	Yes	3 months	No	No	10
Patient 15	58, M	DVT	Prev. DVT, obesity, Spl, FVL	19	No	Platelet infusion TPO-ra	LMWH, apixaban	No	Long term	No	No	Present article

Abbreviations: aPL, antiphospholipid antibodies; AT, antithrombin; Cs, corticosteroid; CVST, cerebral venous sinus thrombosis; DVT, deep vein thrombosis; ITP, immune thrombocytopenia; IVIG, intravenous immunoglobulin; FVL, factor V leiden; LMWH, low-molecular-weight heparin; PE, pulmonary embolism; prev., previous; PVT, portal vein thrombosis; RIX, rituximab; spl, splenectomy; ST, splanchnic thrombosis; TPO-ra, thrombopoietin receptor agonist; UIH, unfractionated intravenous heparin; UVC, umbilical cord catheterization; VCL, venous catheter line; VKA, vitamin K antagonist; VTE, venous thromboembolism.

[a]Includes both VTE- and ITP-associated risk factors.

[b]Full dose of LMWH.

[c]Suggested as specific factor for inducing VTE.

options to increase platelet count, which were also outlined by our review including Cs ($n = 5$), IG therapy ($n = 5$), platelet transfusion ($n = 2$), and Romiplostim and TPO-ra ($n = 2$) (►Table 2). In one case, IVC filter was used in the acute period of VTE. Each option has its own advantages and disadvantages. Cs is commonly considered first-line treatment, as it can provide a stable increase in platelet count in most patients while also being inexpensive, available, and safe to use.[24] However, the platelet count can take several days to reach sufficient levels, and some patients with ITP respond poorly to Cs even in high doses.[25] IG therapy also provides efficient effect, but much like steroids treatment may take several days to sufficiently increase platelet count. In addition, both Cs and IG therapy have previously been shown to increase risk of thrombosis, which could complicate the clinical picture especially in patients with preexisting VTE risk factors.[26,27] Platelet transfusion is the quickest way to increase thrombocytes in patients with ITP and is commonly used in patients with critically low platelet counts especially in CAT.[28] However, platelet transfusion is not without risk either, as platelet transfusion is associated with adverse outcomes such as immune-mediated transfusion reactions.[29] Furthermore, platelet transfusion is not generally effective in the long term for patients with ITP. Finally, TPO-ra is also an efficient method of increasing platelet count but can take several days before a sufficient clinical response and can induce thrombosis much like Cs or IG therapy.[30] In our patient, the choice of treatment in the acute and subacute period fell on platelet transfusion and TPO-ra, respectively, since the patient's platelet count was severely low and he had previously responded poorly to treatment with prednisolone even in high doses.

A key strength of this work is its novelty. This is the first article reporting the long-term use of DOAC in a severe ITP patient with VTE. The main limitation of our article is the potential risk of missing detailed patient data presented in ►Table 2, if the patients are reported in larger studies, but not as case reports.

Conclusion

We have managed the AC treatment in our patient with LMWH and apixaban without any major bleeding and thrombosis complications. Thus, off-label use of DOACs can be considered, as presented in this article, after the acute phase of VTE in patients with stable moderate thrombocytopenia. According to our literature review, the management of VTE in patients with severe ITP ($\leq 35 \times 10^9$/L) is possible without bleeding with no, low-dose, or full-dose AC treatment together with ITP therapy. The initial choice between no, reduced-dose, or full-dose AC therapy seems to depend on the severity of the thrombocytopenia, and the response to treatment to increase thrombocyte count. Until more evidence is available, however, the management of VTE in ITP requires a case-by-case approach.

Statement of Ethics

An ethical review is not required for this type of article. The patient is aware that his clinical details are used in this article. Written consent was given by the patient.

Authors' Contributions

M.H.N. performed the literature review, interpreted the data, and wrote the first draft of the manuscript and approved the final manuscript.

M.V.B. planned the study, supervised for the recruitment of the subject, performed the literature review, interpreted the data, and supervised the writing of the manuscript, and approved the final manuscript.

Data Availability

The data supporting the findings of this study are available on request due to privacy/ethical restrictions.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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