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

Mathias Haargaard Nielsen1  Mustafa Vakur Bor2,3

1 Haematology Unit, Department of Internal Medicine, University Hospital of Southern Denmark, Esbjerg, Denmark
2 Thrombosis Research, Department of Regional Health Research, University of Southern Denmark, Esbjerg, Denmark
3 Thrombosis and Anticoagulation Clinic, Department of Clinical Biochemistry, University Hospital of Southern Denmark, Esbjerg, Denmark

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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 (≤ 35 × 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 (≤ 35 × 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 × 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 × 10^9/L and further discuss risk factors as well as treatment options for venous thromboembolism (VTE).

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 stable. 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
count <100 \times 10^9/L with the exclusion of other causes of
thrombocytopenia. Blood smear and bone marrow investi-
gation showed normal morphology of thrombocytes. The
initial treatment was unsuccessful with high doses of corti-
costeroids (Cs) and was likewise unsatisfactory despite the
addition of rituximab. Good clinical response was achieved
after the patient underwent splenectomy. The patient suf-
f ered from epistaxis, gum bleeding, and tendency to super-
fi cial 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 \times 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% (\textit{\textit{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 admis-
sion included a Wells score of 2 and high D-dimer measure-
ment, suggesting a possible new unprovoked DVT.
Consequently, ultrasonography of the lower extremity con-
fi rmed 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 \times 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 \times 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. After acute treatment, thrombopoietin
receptor agonist (TPO-ra) was administered to address the
persistent thrombocytopenia. LMWH was afterward
changed to apixaban 5 mg \times 2 for 6 months and later reduced
to 2.5 mg \times 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.

\textit{Table 1} The results of the thrombophilia investigation of the patient after the first incident of DVT

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

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 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 \( \text{Table 2}. \) The underlying pathogenesis behind this prothrombotic tendency in patients with ITP is unclear.\(^1\)\(^{14}\) Several different possible causes have been suggested including hyperactive immature platelets,\(^1^5\) platelet microparticles,\(^1^4\) and dysfunction in complement activation.\(^1^6\) 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.\(^1^8\) Risk factors for thrombosis in ITP was discussed in an excellent review by Swan et al.\(^1^9\) VTE risk factors were also seen in 12 patients with severe ITP (\( \text{Table 2} \)). 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.\(^2^0\) While other thrombophilic conditions such as APS are commonly associated with both ITP and thrombotic events,\(^1^7\) 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 risk factors; high thrombotic risk situations requiring AC therapy. This risk score includes two thrombotic-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 \( 19 \times 10^9/L \)) 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.\(^5\)^{21}\(^\) There are different suggested therapeutic

\( \text{Table 2} \)

Venous Thromboembolism in Severe Immune Thrombocytopenia

Nielsen, Bor

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Table 2 Overview of existing literature describing patients with ITP presenting with VTE and a platelet count ≤35 × 10^9/L

| Patient 1 | 83, M | PE | Cancer | 29 | No | Cs + IVIG | UIH, LMWH | Unknown | Long term | No | No | 1 |
| Patient 2 | 31, F | ST | aPL | 14 | Yes, unspecified | IVIG, romiplostim, RIX | LMWH, VKA | Yes | Unknown | No | No | 1 |
| Patient 3 | 83, M | PE, DVT | Unknown | 32 | No | IVIG | LMWH, VKA | Unknown | Long term | No | No | 1 |
| Patient 4 | 66, F | DVT | Obesity, prev. PE | 20 | Yes, unspecified | Yes, unspecified | LMWH, 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, VKA | Unknown | Long term | No | No | 1 |
| Patient 7 | 80, M | PE | Surgery, low AT | 22 | No | No | None | - | No | 11 |
| Patient 8 | 56, F | DVT, PE | IVIG | 14 | IVIG | Cs, spl | LMWH, VKA | Yes | Unknown | No | No | 12 |
| Patient 9 | 76, F | CVST | Prev. PE | 29 | Cs | Cs | LMWH, 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 | 13 |
| Patient 11 | 59, M | DVT | IVIG, Spl, FVL, VCL | 18 | Cs, IVIG | IVIG | VKA | Unknown | Long term | No | No | 13 |
| Patient 12 | 1.5, U | PVT | UVC | 33 | IVIG | No | None | - | No | 13 |
| Patient 13 | 45, F | CVST | Spl, aPL, Romiplostim | 35 | Romiplostim | No | None | - | No | 13 |
| Patient 14 | 54, M | DVT | 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, splanchic 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.

*Includes both VTE- and ITP-associated risk factors.

*Full dose of LMWH.

*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 suffice.\(^{16,26}\) 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 (≤ 35 × 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.

**References**


