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SHORT REPORT

Iatrogenic hemorrhage and extensive venous thromboembolism during iTTP treatment with caplacizumab—A case report

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Abstract

Caplacizumab reduces the need for therapeutic plasma exchange (TPE) during treatment for thrombotic thrombocytopenic purpura (TTP), associates with fewer required TPE, and shortens hospital stay. It is therefore recommended as part of standard care. However, the treatment effects on hemostasis may complicate initial management. We present a case of a woman with immune-mediated TTP who developed an intrathoracic hemorrhage on caplacizumab treatment after replacement of her central venous catheter. Reduced von Willebrand factor (vWF):glycoprotein Ib mutant (GPIbM) activity was reversed using vWF concentrate and the bleeding stopped. Unfortunately, vWF substitution in combination with caplacizumab discontinuation likely contributed to subsequent extensive venous thromboembolism. Risk-reducing strategies against both bleeding and thrombosis are crucial during caplacizumab treatment, and emergency vWF substitution increases the already high risk of thrombosis associated with TPE.

KEYWORDS
adverse drug event, hemorrhage, thrombotic thrombocytopenic purpura, venous thromboembolism, von Willebrand factor

1 | INTRODUCTION

The treatment of the rare, potentially fatal condition, thrombotic thrombocytopenic purpura (TTP) has greatly improved over the last two decades with the cornerstones being immediate therapeutic plasma exchange (TPE) at high clinical suspicion followed by immunosuppression with steroids and rituximab as soon as diagnosis is confirmed [1].

Caplacizumab is a Nanobody® (single-domain antibody), blocking the interaction of the von Willebrand factor (vWF) at the A1 domain of the glycoprotein Ib-IX-V receptor on platelets, preventing platelet adhesion to ultralarge von Willebrand multimers and microthrombi formation [2]. Treatment reduces the time taken for platelet count to return to normal and associates with fewer required TPE and shorter hospital stay [3]. Consequently, the drug has been introduced as a complement to TPE after approval by European Medicines Agency (EMA) in 2018. Caplacizumab is administered as daily injections for 30 days, using a fixed dose (age >12 years, weight >40 kg). In the clinical trials, bleedings, mainly from the nose and gingiva, were common (frequency 1/100–1/10) but considered manageable [4]. Since the approval by EMA, real-world data have been published from European centers, suggesting that ADAMTS13 activity can be measured to guide
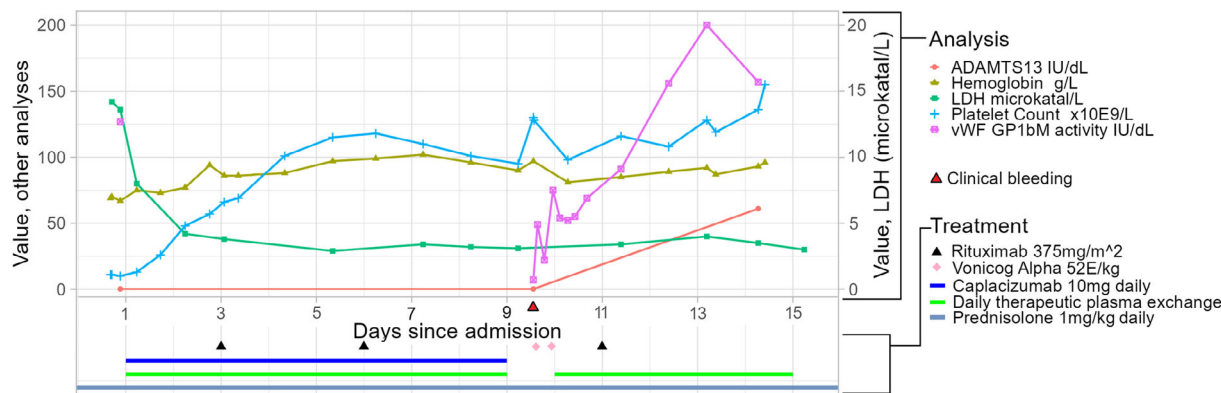
FIGURE 1 Overview of treatments and laboratory parameters during the first 17 days after hospital admission. The mediastinal bleeding happened on Day 10. vWF, von Willebrand factor. LDH, lactate dehydrogenase

caplacizumab treatment duration [5]. However, laboratory tests monitoring hemostasis to estimate bleeding risk during caplacizumab treatment are still lacking [6–8].

2 | CASE PRESENTATION

We present here a case of immune-mediated TTP (iTTP), where caplacizumab treatment was complicated by a traumatic bleeding in tandem with venous thromboembolism.

A previously healthy woman in her 30s of Asian origin presented with nausea, dizziness, and vomiting since a few days at the emergency room in a community hospital in Stockholm, Sweden. Initial physical examination was unremarkable. However, shortly after arrival the patient suddenly became hemiparetic. An immediate computer tomography (CT) of the brain and angiography of cerebral arteries ruled out bleeding, thrombosis, and embolism. Blood samples revealed severe anemia (hemoglobin 6.9 g/dL) and thrombocytopenia (11×10^9/L), as well as increased lactate dehydrogenase (852 U/L) and bilirubin (3.276 mg/dL) concentration. Creatinine concentration was normal (0.8136 mg/dL).

The patient was highly suspected of having TTP, with a PLASMIC score of 6, and she was urgently transferred to Karolinska University Hospital, the tertiary referral hospital [9]. Plasma infusion was administered at the emergency room, and TPE with octaplasLG was started 3 h after admission (9 h after initial admission at the community hospital). An ADAMTS13 activity of 0.2 IU/dL (40–130 IU/dL) and a high titer of ADAMTS13 antibodies (>20 U/L) confirmed the diagnosis of iTTP. The central venous catheter was placed in the right femoral vein. Treatment continued with daily TPE (1.5 plasma volumes), the equivalent of 1 mg/kg/day of prednisolone and weekly doses of 375 mg/m² rituximab (two doses during the first week). Caplacizumab, with a dose of 10 mg/day, was added on Day 2. The first dose was given intravenously, and subsequent doses as subcutaneous injections. Neurological examination 15 h after the first TPE revealed substantial improvement in right side motor function. The platelet count increased promptly to 101×10^9/L within 4 days but did not exceed 150×10^9/L until Day

19 (Figure 1). Low molecular weight heparin prophylaxis was omitted due to caplacizumab treatment.

On Day 10, the central venous catheter was replaced to the right jugular vein under ultrasound guidance, due to obstructed flow during apheresis. Unfortunately, the procedure was complicated by a bleeding, likely initiated by perforation of the superior vena cava by the guidewire. The bleeding caused subcutaneous swelling in the right supraclavicular fossa and on the right side of the neck. A CT demonstrated blood extending to the mediastinum and neck with dislocation of the trachea. Blood samples were promptly obtained to assess coagulation as the patient had additional subcutaneous hematomas and vaginal bleedings. Hemoglobin concentration dropped from 9.7 g/dL on Day 10 to 8.1 g/dL on Day 11, but no erythrocyte transfusions were needed. Platelet count was almost normal at 130×10^9/L, but whole blood analysis with platelet function analyzer (PFA)-100® demonstrated impaired primary hemostasis with a prolonged closure time for both adenosine diphosphate (ADP)- and epinephrine-coated membranes (212s, reference <110s and 224s, reference <150s, respectively). Prothrombin time, international normalised ratio (PT-INR) and activated partial thromboplastin time remained normal, but fibrinogen concentration was decreased to 120 mg/dL with elevated d-dimer concentration of 25,600 ng/mL. The vWF activity in plasma was markedly decreased, 7 IU/dL (50–190 IU/dL), but the vWF antigen and FVIII:C were both normal (92 and 113 IU/dL, respectively). ADAMTS13 in plasma remained suppressed at 0.2 IU/dL while the antibody titer had decreased from >20 to 1.6 U/L.

Caplacizumab was immediately discontinued, and the bleeding was treated with recombinant human vWF, vonicog alfa, with a target vWF activity of 50 IU/dL. In total, two doses of vonicog alfa (52 IU/kg per dose) were given the first day after the trauma. No progression of the hematoma was evident on clinical examination and follow-up CT. vWF activity was promptly normalized and remained so the following days.

On the same day of the bleeding, an ultrasound of the right leg had been performed due to pain and discomfort. The ultrasound demonstrated a distal deep venous thrombosis (DVT) and suspected thrombosis on the central venous catheter. DVT treatment was initiated 1 day later with a low dose of dalteparin when the bleeding had

stabilized. Two days later, a CT was performed because of abdominal pain and revealed progression of the thrombosis proximally up to the distal inferior vena cava and pulmonary embolism. Dalteparin dose was increased to 200 IU/kg and the thrombosis stabilized.

Daily TPE was continued for a total of 16 treatments (until Day 17). In all, the patient received eight doses of caplacizumab but treatment was never resumed after the bleed. ADAMTS13 activity was normalized in plasma on Day 15. The patient was discharged on Day 25, she was at that timepoint fully mobilized to continue rehabilitation at home.

3 | DISCUSSION

While the addition of caplacizumab to the treatment of iTTP results in faster responses, it also complicates the balance between bleeding and thrombosis that is integral to the initial management of this condition. Treatment-related hemorrhages during clinical trials have been mostly mild [4], but the current case and several other real-world reports demonstrate that caplacizumab can contribute to significant bleeding events in the acute phase [3, 6, 10]. Central venous catheterization rarely results in severe bleeding [11], especially when performed in the internal jugular vein under ultrasound guidance [12]. Thus, impaired primary hemostasis due to caplacizumab-mediated suppression of vWF interaction with platelets (glycoprotein Ib-IX-V receptor) likely contributed to the extent of the hemorrhage. Inhibition of vWF binding to platelets was rapidly and readily detected by PFA-100 assessments despite almost normal platelet count at the time of bleeding.

Currently, no recommendations for managing hemorrhage during caplacizumab treatment exist beyond drug discontinuation [10]. While platelet-binding capacity of vWF is restored within 1–2 days after discontinuing caplacizumab [2], additional administration of vWF concentrate to rapidly reverse the caplacizumab-mediated suppression of vWF activity is mechanistically appealing during acute bleeding. However, this approach has not been systematically studied and may increase the risk of thromboembolism [2]. Since caplacizumab treatment causes profound suppression of vWF activity in most patients, vWF:glycoprotein Ib mutant (GPIbM) assays have no value to support initial management [13]. Instead, a risk–benefit analysis should underlie the decision to administer vWF concentrate as a countermeasure. To avoid prothrombotic increases in FVIII activity, our patient was treated with a pure vWF concentrate (vonicog alfa) instead of Haemate [14]. Notably, since vonicog alfa is a recombinant vWF concentrate, it contains ultralarge vWF multimers [15]. These multimers may theoretically exacerbate TTP due to deficient ADAMTS13 activity in circulation. However, in our patient, platelet counts remained stable and no arterial thrombosis or iTTP symptoms developed following vonicog alfa administration. Discontinuation of caplacizumab and administration of two doses of vonicog alfa resulted in supranormal vWF activity (Figure 1). Therefore, a single, reduced dose of vonicog alfa would likely have been sufficient.

Real-world data suggest that discontinuing TPE before platelet counts normalize may be appropriate for patients receiving capla-

cizumab treatment [8]. Thus, it would have likely been safe to discontinue TPE once the catheter flow was obstructed, especially considering the platelet count had risen to 130×10^9/L. Additionally, extending the interval between the caplacizumab doses may be feasible without compromising efficacy [7], and could potentially reduce bleeding risk in patients with lower body weight. Another preventive measure worth considering would have been administering TPE through a peripheral catheter.

Based on local guidelines, low molecular weight heparin (LMWH) prophylaxis was withheld due to concurrent caplacizumab treatment. Unfortunately, the patient developed a catheter-related DVT, which progressed due to delayed anticoagulant treatment while managing the bleeding. The incidence of venous thromboembolism (VTE) in iTTP patients is reported as high as 10%–15%, and caplacizumab does not appear to reduce the risk [16]. Previous studies indicate that these events are often associated with central venous catheters [17], and occur more frequently in patients not receiving LMWH prophylaxis [16, 17]. Consequently, experts [12] recommend considering pharmacologic VTE prophylaxis once platelet count exceeds 50×10^9. Even so, this recommendation lack robust evidence, and LMWH prophylaxis may have exacerbated the bleeding in our patient.

To improve clinical management of iTTP, future studies should address the optimal use of VTE prophylaxis during caplacizumab treatment, as well as the efficacy and safety of vWF concentrate as an emergency countermeasure in case of bleeding.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

Since this is a report of a single case, no external ethical approval has been sought.

PATIENT CONSENT STATEMENT

The patient provided informed consent for the use of her clinical history in this case report.

CLINICAL TRIAL REGISTRATION

The authors have confirmed clinical trial registration is not needed for this submission.

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