Hong Kong College of Physicians
Case report for Interim Assessment
Specialty Board of Advanced Internal Medicine (AIM)

For AIM Training, case reports should be submitted in the prescribed format together with the application form for Interim Assessment at least EIGHT Weeks before the date of Interim Assessment

Name of candidate (print and sign): **LEE Steffi Kristen**
Hospital and Unit: **HHH Medicine** Specialty: **AIM** and **Geriatrics**
Name of supervisor (print and sign): **Dr. WONG Tin Chiu**
Date(s) and place of patient encounter: **November 2022, TKOH**
Date of report submission:

Case report

Note: Failure to follow the prescribed format (including the number of words) results in a FAILURE mark (score between 0 and 4) for the Case Report.

Title: Two Sides of the Same Coin: A Paradox of Bleeding and Clotting

Case history:

A 72-year-old woman was admitted for sudden-onset weakness over her left upper and lower limbs associated with numbness over the same area, drooling of saliva, and slurring of speech at around 1:15pm. Her symptoms had resolved by the time she arrived at the Accident & Emergency Department for assessment at 2pm. She had no fever, headache, visual disturbance, or vomiting. There was no history of recent head trauma, and she had no prior history of similar symptoms.

Her medical history was notable for hypertension, hyperlipidemia, coronary artery disease, and endometrial polyps, for which she had undergone hysteroscopy and curettage (H&C) one week earlier. Medications included amlodipine, aspirin, atorvastatin, bisoprolol, and famotidine. She had no known drug allergies. She was a housewife who lived with her husband and two children. She did not smoke or drink alcohol.

On examination, she was afebrile with blood pressure 136/72mmHg, pulse 80 beats per minute (bpm), respiratory rate 16 breaths per minute, and oxygen saturation 100% in ambient air. Glasgow Coma Scale was full and there were no focal neurological deficits or meningeal signs.

There were no carotid bruits, and the chest, cardiovascular, and abdominal exams were unremarkable. Bruises were noted over her left wrist and bilateral knees. Per rectal examination was empty.

Further questioning revealed that she had experienced bruising over her limbs and trunk without noticeable trauma for the past month. She had also had on-and-off vaginal bleeding since the H&C performed one week earlier.

Non-contrast computed tomography scan of the brain did not show any focal abnormalities. Chest x-ray was unremarkable. Electrocardiography showed sinus rhythm at 64 bpm. Blood tests demonstrated severe thrombocytopenia with a platelet level of 18 x 10^9/L and mild anemia with a hemoglobin level of 10 g/dL. White cell count was normal, as were liver and renal function tests. Urine dipstick was negative for red cells and protein. Further tests revealed findings suggestive of hemolysis, including elevated lactate dehydrogenase (604 U/L) and reticulocyte count (6.4%), undetectable haptoglobin (< 0.10 g/L), and schistocytes in the peripheral smear. Coomb's test was negative. Clotting profile and fibrinogen were normal (INR 1.0, APTT 22 seconds, fibrinogen 2.57 g/L).

Aspirin was withheld on admission due to thrombocytopenia. As the initial presentation was suspicious for thrombotic thrombocytopenic purpura (TTP) with PLASMIC score of 6 (figure 1), hematology team was consulted and she was started on empirical steroids with intravenous (IV) hydrocortisone 100mg every 6 hours while testing for ADAMTS-13 activity was underway. Results of ADAMTS-13 testing showed markedly reduced activity (< 0.02%), which supported the diagnosis of immune TTP.

She subsequently underwent five sessions of therapeutic plasma exchange (TPE) with fresh frozen plasma in the intensive care unit, after which her platelet count rebounded to a peak of 307 x 10^9/L before dropping gradually again to 52 x 10^9/L. Repeat testing of ADAMTS-13 showed persistently low activity (< 0.02%). Two additional sessions of TPE were performed, and she was given a cycle of Rituximab. Platelet count rose again and remained stable between 160-300 x 10^9/L. IV hydrocortisone was switched to oral prednisolone 40mg daily and tapered at a dose of 10mg per week. She was discharged from hospital 28 days after initial admission.

After discharge, she received three more cycles of Rituximab. After one week on Prednisolone 10mg daily, the dose was decreased to 5mg for one final week before steroid treatment was stopped completely 62 days

after the last TPE. Her platelet count remained stable at around 200 x 10^9/L. She had no recurrence of any focal neurological deficits.

Discussion and literature review

TTP is a rare but important hematological entity that can become rapidly fatal if unrecognized and untreated. The classic pentad of TTP (fever, neurological deficit, thrombocytopenia, microangiopathic hemolytic anaemia, and renal impairment) is only present in its entirety in less than 10% of patients [1]. However, an initial presentation with neurological symptoms, like in our patient, was not uncommon. One study involving 78 patients with TTP found that 67% presented with some form of neurological abnormality, including headache, dizziness, slurred speech, numbness, weakness, seizures, and even coma [2]. Although many neurological symptoms were fluctuating, like those found in our patient, another review involving 109 patients with TTP found that nearly one-third of those with neurological symptoms were later found to have image-confirmed ischemic stroke, a finding which was associated with increased age and cardiovascular risk factors such as smoking and hypertension [1].

The pathophysiology of TTP involves ADAMTS-13 deficiency, the vast majority of which is due to acquired inhibitors or auto-antibodies against ADAMTS-13 (known as immune TTP), such as in our patient. A small proportion of TTP is due to genetic deficiency of the ADAMTS-13 protein (known as hereditary or congenital TTP). ADAMTS-13 is responsible for the breakdown of von Willebrand factor (vWF). Without ADAMTS-13, uncleaved vWF form ultra-large multimers, leading to unrestricted promotion of platelet adhesion and aggregation, which in turn leads to the unique dichotomy of simultaneous thrombotic (due to intraluminal thrombosis) and bleeding (due to platelet consumption and dysfunction) tendencies.

Diagnosis of TTP depends upon establishment of ADAMTS-13 deficiency (with ADAMTS-13 activity < 10% being highly supportive of a diagnosis of TTP). However, ADAMTS-13 testing is neither universally nor rapidly available. As such, clinical risk assessment models such as the PLASMIC score have been established to aid in decision-making for treatment initiation before definitive ADAMTS-13 test results are available – a crucial element in identifying patients who are likely to have TTP in order to facilitate early treatment (especially therapeutic plasma exchange (TPE)), in order to reduce mortality and adverse outcomes. A

systemic review including over 900 patients with a median TTP prevalence of 35% showed that PLASMIC score equal to or greater than 5 was associated with high sensitivity and negative predictive value for TTP [3], making the PLASMIC score a useful screening tool for this disease. Our patient, whose PLASMIC score was 6, had a high pre-test probability for TTP, and in retrospect, we could have considered initiating TPE based on her PLASMIC score alone rather than waiting for the results of the ADAMTS-13 testing, which would have resulted in starting TPE one day earlier.

Treatment of TTP includes several modalities, namely, plasma exchange, immunosuppressive agents including glucocorticoids and rituximab, and newer specific therapies such as the anti-VWF monoclonal antibody, caplacizumab. The mainstay of TTP treatment is therapeutic plasma exchange (TPE), which allows for the removal of the autoantibodies inhibiting ADAM-TS13 and the ultra-large VWF multimers promoting platelet aggregation with subsequent replacement by donor plasma containing functional ADAM-TS13 protein. Glucocorticoids are also recommended for use as first-line therapy along with TPE for all patients with TTP for their immunosuppressive effect in reducing production of the ADAMTS-13 inhibitor autoantibody. While Rituximab is also recommended by the ISTH guidelines as initial therapy for TTP confirmed by ADAMTS-13 testing, this is mainly based on findings from observational studies, such as one meta-analysis including 570 patients from nine different studies which found that the addition of Rituximab was able to prevent relapses and lower mortality rates compared to conventional therapy with TPE and glucocorticoids alone [5]. However, in the Hospital Authority, Rituximab for treatment of TTP is a self-financed item, which may be a limiting factor for its use as an initial treatment, as in our patient, where Rituximab was only added after the platelet count persistently declined despite initial treatment with TPE and glucocorticoids. In 2019, a new specific treatment for TTP was approved by the US Food and Drug Administration – Caplacizumab, a monoclonal antibody against VWF, which targets the VWF domain that interacts with platelets and blocks platelet-VWF interactions. It does not, however, correct the underlying ADAMTS-13 deficiency. Addition of Caplacizumab to conventional therapy in a randomized trial involving 145 patients demonstrated impressive results including lower mortality, faster normalization of the platelet count (and hence fewer days of TPE), fewer exacerbations, and shorter hospitalizations, although it was also

associated with higher rates of bleeding [6]. Unfortunately, Caplacizumab is yet to be available in Hong Kong, and, as in our patient, it seems that we will have to rely on older therapies for now.

In conclusion, TTP is a rare but potentially fatal disease in which early diagnosis and treatment could mean the difference between near-certain mortality and near-certain survival. Early use of clinical risk assessment models such as PLASMIC score can help to assess pre-test probability of TTP and guide decision-making on initiation of life-saving treatment while awaiting definitive ADAMTS-13 testing.

Tables and figures (where applicable) (no more than two figures)

Figure 1:

PLASMIC Score	*Point*
Platelet count < 30 x 10^9/L	1
Hemolysis (retic > 2.5%, undetectable haptoglobin, or indirect bilirubin > 34 umol/L)	1
MCV < 90 fL	1
INR < 1.5	1
Cr < 177 umol/L	1
No active cancer in the preceding year	1
No history of solid organ or hematopoietic stem cell transplant	1

6-7 points: high risk

5 points: intermediate risk

0-4 points: low risk

Reference (not more than 10)

1. Memon R, Sui J, Lin C, Zheng XL. Cerebral Infarction in Immune Thrombotic Thrombocytopenic Purpura Is Associated with Old Age, Hypertension, Smoking, and Anti-ADAMTS13 Ig, But Not with Mortality. TH Open. 2021 Jan 13;5(1):e1-e7.
2. Page EE, Kremer Hovinga JA, Terrell DR, Vesely SK, George JN. Thrombotic thrombocytopenic purpura: diagnostic criteria, clinical features, and long-term outcomes from 1995 through 2015. Blood Adv. 2017 Apr 6;1(10):590-600.
3. Paydary K, Banwell E, Tong J, Chen Y, Cuker A. Diagnostic accuracy of the PLASMIC score in patients with suspected thrombotic thrombocytopenic purpura: A systematic review and meta-analysis. Transfusion. 2020 Sep;60(9):2047-2057.
4. Owattanapanich W, Wongprasert C, Rotchanapanya W, Owattanapanich N, Ruchutrakool T. Comparison of the Long-Term Remission of Rituximab and Conventional Treatment for Acquired Thrombotic Thrombocytopenic Purpura: A Systematic Review and Meta-Analysis. Clin Appl Thromb Hemost. 2019 Jan-Dec.
5. Scully M, Cataland SR, Peyvandi F, Coppo P, Knöbl P, Kremer Hovinga JA, Metjian A, de la Rubia J, Pavenski K, Callewaert F,

Biswas D, De Winter H, Zeldin RK; HERCULES Investigators. Caplacizumab Treatment for Acquired Thrombotic Thrombocytopenic Purpura. N Engl J Med. 2019 Jan 24;380(4):335-346.

6. Zheng XL, Vesely SK, Cataland SR, Coppo P, Geldziler B, Iorio A, Matsumoto M, Mustafa RA, Pai M, Rock G, Russell L, Tarawneh R, Valdes J, Peyvandi F. ISTH guidelines for treatment of thrombotic thrombocytopenic purpura. J Thromb Haemost. 2020 Oct;18(10):2496-2502.

No of words in Case History and Discussion (excluding references):___1952___(should be between 1000-2000)

Declaration

I hereby declare that the case report submitted represents my own work and adheres to the prescribed format. I have been in clinical contact with the case selected. The case report has not been submitted to any assessment board or publication and it is NOT related to my second specialty(ies), if any. My consent is hereby given to the College to keep a copy of my case report, in written and/or electronic, at the College Secretariat and allow the public to have free access to the work for reference.

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(signature of Trainee)

Endorsed by Supervisor *

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(signature of Supervisor)

* Supervisors must go over the Case Report with the Trainees, advise Trainees whether further amendments are necessary, review the Originality/Similarity Report prepared by Trainees, adherence to the required format, sign on the report and remind Trainees on issues related to copyright and plagiarism.