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): Ho Man Yan Audrey
Hospital and Unit: POH Specialty: M&G
Name of supervisor (print and sign): Dr. Chan Yuk Kit
Date(s) and place (hospital) of patient encounter: 2/2/2024 in POH SURG Ward
Date of report submission: 7/3/2024

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: A case of immune thrombocytopenia with relapse

Case history:

A 49-year-old lady has a history of recurrent urinary tract infections due to staghorn stone. She was found to have a platelet count of $12x10^9$/L during the pre-operative assessment for renal stone operation in November 2022.

Her initial peripheral blood smear showed occasional large platelets and was otherwise unremarkable. Vitamin B12 and folate levels were normal. Anti-hepatitis C virus antibody and Anti-human immunodeficiency (HIV) virus were negative. Anti-nuclear antibody titer was 80 but Anti-double stranded DNA, C3, and C4 were all negative. Serum protein electrophoresis showed no abnormal band.

She was managed as immune thrombocytopenia with oral prednisolone 30mg twice daily. Prednisolone was slowly tapered and was stopped in July 2023 as her platelet level normalized. She reported side effects of prednisolone including weight gain, central obesity, insomnia, and moon face.

Passed at Council Meeting on 24 Oct 2019

During the pre-operative assessment for percutaneous nephrolithotomy scheduled in February 2024, she was found to have thrombocytopenia again, with a platelet level of 16 $x10^9$/L. She was then admitted to the surgical ward for an inpatient hematology consultation. She was started on intravenous immunoglobin 0.4g/kg/day for 5 days. As she did not have any bleeding symptom, platelet transfusion was not given.

Further management options for relapse of immune thrombocytopenia were discussed with the patient. These include starting prednisolone 1g/kg/day with Mycophenolate Mofetil (MMF) 500mg BD as steroid-sparing agent, referral to the surgical department for elective splenectomy, or starting self-finance Eltrombopag. As she could not tolerate the side effects of high-dose steroid, she only agreed to start low-dose prednisolone with MMF. She declined the option of splenomegaly and self-finance Eltrombopag due to surgical risk and financial difficulty. Bone marrow examination was offered and was declined by the patient.

On discharge, her platelet level was $117x10^9$/L. She was started on prednisolone 20mg daily and Mycophenolate Mofetil 500mg twice daily. As the most recent anti-hepatitis B core antibody was intermediate, she was also started on entecavir. Her surgical procedure was postponed.

She was followed up a week later and her platelet level was normalized. The dosage of MMF was increased to 1g twice daily and the dosage of prednisolone was tapered. The short-term treatment target was to maintain a reasonable platelet level to allow surgical procedure.

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Discussion and literature review

Immune thrombocytopenia(ITP) is an acquired autoimmune disorder causing platelet destruction and impaired platelet production.(1) It has a prevalence of 0.9-2.6 per 10,000.(2)

In clinical practice, ITP is a diagnosis by exclusion and it is best confirmed by clinical response to ITP treatment.(2, 3) The diagnosis can be made if the platelet count is less than $100x10^9$/L after excluding other differential diagnoses.(2) Some differentials of thrombocytopenia include bone marrow diseases such as myelodysplastic syndrome or leukaemia, drug-induced thrombocytopenia, splenomegaly, inherited thrombocytopenia, and infection.(3, 4) ITP can be classified according to the duration of the disease. A duration of 3-12 months is classified as a persistent disease, whereas a duration lasting more than 12 months is classified as a chronic disease.(4)

Initial workup includes blood tests for blood count, peripheral blood smear, coagulation profile, autoimmune markers, hepatitis markers, HIV test, thyroid function test, ultrasound for splenomegaly, and Helicobacter Pylori testing using urea breath test or stool antigen test.(2, 4) For case refractory to treatment or if the patient experiences atypical symptoms such as weight loss, hepatosplenomegaly or enlarged lymph nodes, a bone marrow examination with cytogenetic study may be indicated.(2, 3)

Commonly used medical therapies for ITP include corticosteroid, intravenous immunoglobulin(IVIg), anti-D, Rituximab, Thrombopoietin Receptor Agonist(TPO-RA), and immunosuppressive agents.(4)

IVIg provides a rapid but short-lived effect on platelet levels which only lasts for 2-4 weeks after administration.(2) It is useful in situations where haemostasis needs to be achieved or when surgery cannot not be delayed.(2)

Three TPO-RAs are currently available, including Eltrombopag, Avatrombopag, and Romiplostim.(4) The effectiveness of Eltrombopag in overall platelet response and reducing the risk of significant bleeding was demonstrated in a meta-analysis.(5) Some of the side effects of Eltrombopag include elevation of aspartate transaminase level, headache,

anaemia, gastrointestinal discomfort, arthralgia, and upper respiratory tract infection.(5) Thrombosis, one of the potential side effects of TPO-RA, was not significantly higher in ITP patients receiving TPO-RA, although most studies withheld or stopped TPO-RA when platelet level reached 200x 10^9/L.(6)

Evidence of other medical therapies including immunosuppressive agents (such as Mycophenolate Mofetil, cyclosporin A, azathioprine, cyclophosphamide), danazol, and dapsone are less robust.(4)

Combination of medical therapies for ITP has also been studied. It was shown in a meta-analysis that Mycophenolate Mofetil(MMF) gives an overall and complete response rate of 50% and 32% respectively in treating patients with ITP.(7) Compared to corticosteroid therapy alone, combined therapy with MMF and corticosteroid significantly increased platelet levels and caused fewer treatment failures.(7) The combination of Eltrombopag and rituximab resulted in the greatest remission rate among other treatment options for ITP, compared to placebo or dexamethasone alone.(8) In refractory ITP, a combination of TPO-RA, immunosuppressants such as MMF or cyclosporin, and IVIg give promising results.(3)

The 2018 recommendations of a joint working group recommended corticosteroid as a first-line therapy for ITP.(2) During an emergency of severe bleeding, IVIg should be administered in addition to corticosteroid.(2) Platelet concentrates, rituximab, or TPO-RA should be considered in case of life-threatening bleeding.(2)

Similarly, the 2019 American Society of Haematology guideline suggested corticosteroid (either prednisolone 0.5-2.0 mg/kg/day or dexamethasone 40mg per day for 4 days) as initial therapy in newly diagnosed ITP with a platelet count of less than $30x10^9$/L.(1) For those who are dependent on corticosteroid or are refractory to initial treatment, rituximab is considered as a second-line therapy in addition to TPO-RA and splenectomy.(1) Immunosuppressive agents including azathioprine, cyclophosphamide, cyclosporin A, and MMF were not formally evaluated in the guideline.(1)

Splenectomy is a surgical treatment for ITP which may provide long-term relapse-free remissions.(4) It is recommended to wait for at least 12 to 24 months from diagnosis before considering splenectomy due to the possibility of remission.(4) The American guideline is in favour of TPO-RA or rituximab over splenectomy during the first 12 months of disease as the chance of spontaneous remission is higher.(1) Those who underwent splenectomy should receive appropriate vaccinations.(4)

Treatment options should be individualized, taking the patient's comorbidities, preference, cost, duration of disease, and number of bleeding episodes into consideration.(1) In this case, the patient had a relapse of ITP. Before starting treatment, the diagnosis of ITP should be reconsidered. Bone marrow examination is considered in her case to rule out other secondary causes of thrombocytopenia. Early control of the disease is required as repeated surgical interventions are expected in the future for recurrent infection due to renal stones. Combination therapy with MMF and prednisolone was offered as it may give a better response than corticosteroid therapy alone with fewer steroid-related side effects. Eltrombopag is a reasonable choice of second-line therapy although it is not given in this case due to financial concern. As the chance of remission is lower in chronic ITP, the option of splenectomy should be discussed with the patient again if she fails to achieve remission with medical therapy.

In summary, this case illustrates the diagnostic process and treatment options for ITP with relapse. The choice of medical or surgical therapy should be individualized, guided by evidence of treatment, disease duration, preference, cost, and risks and benefits of each option.

Passed at Council Meeting on 24 Oct 2019

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

Reference (not more than 10)

1. Neunert C TD, Arnold DM, Buchanan G, Cines DB, Cooper N, Cuker A, Despotovic JM, George JN, Grace RF, Kühne T, Kuter DJ, Lim W, McCrae KR, Pruitt B, Shimanek H, Vesely SK. . American Society of Hematology 2019 guidelines for immune thrombocytopenia. Blood Adv. 2019 Dec 10;3(23):3829-3866. doi: 10.1182/bloodadvances.2019000966. Erratum in: Blood Adv. 2020 Jan 28;4(2):252. PMID: 31794604; PMCID: PMC6963252.
2. Matzdorff A MO, Ostermann H, Kiefel V, Eberl W, Kühne T, Pabinger I, Rummel M. . Immune Thrombocytopenia - Current Diagnostics and Therapy: Recommendations of a Joint Working Group of DGHO, ÖGHO, SGH, GPOH, and DGTI. Oncol Res Treat. 2018;41 Suppl 5:1-30. doi: 10.1159/000492187. Epub 2018 Sep 19. PMID: 30235458.
3. Vianelli N, Auteri G, Buccisano F, Carrai V, Baldacci E, Clissa C, et al. Refractory primary immune thrombocytopenia (ITP): current clinical challenges and therapeutic perspectives. Ann Hematol. 2022;101(5):963-78.
4. Provan D AD, Bussel JB, Chong BH, Cooper N, Gernsheimer T, Ghanima W, Godeau B, González-López TJ, Grainger J, Hou M, Kruse C, McDonald V, Michel M, Newland AC, Pavord S, Rodeghiero F, Scully M, Tomiyama Y, Wong RS, Zaja F, Kuter DJ. Updated international consensus report on the investigation and management of primary immune thrombocytopenia. Blood Adv. 2019 Nov 26;3(22):3780-3817. doi: 10.1182/bloodadvances.2019000812. PMID: 31770441; PMCID:

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5. Ahmed HAW, Masoud AT, Han J, Adel Sofy A, Saeed Ahmed A, Abdesattart AT, et al. Eltrombopag Effectiveness and Tolerability in Chronic Immune Thrombocytopenia: A Meta-Analysis. Clin Appl Thromb Hemost. 2021;27:10760296211005555.
6. Tjepkema M, Amini S, Schipperus M. Risk of thrombosis with thrombopoietin receptor agonists for ITP patients: A systematic review and meta-analysis. Crit Rev Oncol Hematol. 2022;171:103581.
7. Abdelwahab OA, Mechi A, Gahlan S, Hamadein FE, Kadhim H, Ismail D, et al. Efficacy and safety of mycophenolate mofetil in patients with immune thrombocytopenic purpura: a systematic review and meta-analysis. Clin Rheumatol. 2024;43(2):621-32.
8. Zhou H, Fan J, He J, Hu S. Comparative efficacy of 19 drug therapies for patients with idiopathic thrombocytopenic purpura: a multiple-treatments network meta-analysis. Ann Hematol. 2022;101(5):953-61.

No of words in Case History and Discussion (excluding references): 1195
(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.

_____
(signature of Trainee)

Endorsed by Supervisor *

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(signature of Supervisor)

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sign on the report and remind Trainees on issues related to copyright and plagiarism.