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CASE REPORT

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Thrombocytopenia and hyperthyroidism: A case report and literature review

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Key Clinical Message

Immune thrombocytopenic purpura (ITP) is very challenging to diagnose with concurrent comorbidities affecting platelet count including PAH and autoimmune thyroid disease. ITP resolution can be achieved with tailored treatment of the underlying conditions to avoid adverse events.

Abstract

Immune thrombocytopenic purpura (ITP) is an autoimmune disorder characterized by a platelet count of $<100\times10^9$/L in the absence of other causes of thrombocytopenia. It is classified as primary or idiopathic and secondary due to various coexisting conditions, including autoimmune thyroid diseases. It is especially challenging when the patient has comorbidities that affect platelet count easily, leading to anchoring bias. The first-line treatment of ITP is corticosteroids, and it is also recommended to treat the primary causes of secondary ITP. Here, the authors report a case of secondary ITP in a patient with a recent diagnosis of Grave's disease and a history of idiopathic pulmonary hypertension with baseline chronic thrombocytopenia, possible mechanisms, and treatment strategies with a multidisciplinary approach.

KEYWORDS

autoimmune disease, Grave's disease, immune thrombocytopenia, pulmonary arterial hypertension, thyroid disease

1 | INTRODUCTION

Immune thrombocytopenic purpura (ITP) is an autoimmune disorder characterized by a platelet count of $<100\times10^9$/L. It can be categorized as primary ITP, defined without underlying precipitants, and secondary ITP, which includes all forms of ITP other than primary. Investigations for thrombocytopenia should be done to identify the etiology of secondary ITP, which has been associated with Helicobacter pylori infection, viral infection including hepatitis C, human immunodeficiency virus (HIV), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), autoimmune diseases including systemic lupus erythematosus (SLE), antiphospholipid syndrome, and autoimmune thyroid diseases.[1,2] Secondary ITP association with Graves' disease is not uncommon; however,

the treatment is still controversial. Here, the authors report a case of secondary ITP in a patient with a recent diagnosis of Grave's disease and a history of idiopathic pulmonary hypertension with baseline chronic thrombocytopenia whose platelet count improved after receiving radioactive iodine.

2 | CASE PRESENTATION

A 24-year-old female with a past medical history of idiopathic pulmonary hypertension (well-controlled with triple oral therapy including sildenafil, epoprostenol, and ambrisentan), chronic right-sided heart failure WHO class III (based on right heart catheterization), and chronic thrombocytopenia due to ambrisentan with a baseline platelet count of 42,000–60,000/μL. She presented for evaluation for a month of worsening shortness of breath, generalized fatigue, weakness, and palpitations. Her routine work-up showed hyperthyroidism (TSH <0.01 mcIntUnit/mL, Free T4 2.94 ng/dL). She denied abnormal menstruation, bowel habit changes, and weight changes. She started on methimazole (MMI) 5 mg daily. A week later, she presented again for a regular follow-up, where she was found to have worsening thrombocytopenia to 13,000/μL with no signs of acute bleeding. She was admitted for further evaluation. She reported intermittent self-resolved epistaxis for a couple of days and palpitation but denied weight loss, anxiety, flushing, chest discomforts, sweating, irritability, melena, hematochezia, or obvious source of bleeding. Physical examinations revealed tachycardia with a heart rate of 108 beats/minute, loud P2 on auscultation, and mild diffuse thyroid enlargement without bruit or tenderness. No tremors or signs of thyroid eye disease were observed; her clinical examination was otherwise unremarkable. Initial laboratory results were significant for anemia with a hemoglobin level of 9.8 g/dL, thrombocytopenia with a platelet count of 13,000/μL, thyroid stimulating hormone (TSH) <0.01 mcIntUnit/mL, Free T4 2.47 ng/dL, Free T3 4.58 pg/mL, thyroid stimulating immunoglobulin (TSI) 346%baseline, TSH receptor Ab 3.13 IntUnits/L, antithyroid peroxidase (anti-TPO) >600 IntUnits/mL and positive direct antiplatelet antibody. The iron panel was consistent with iron deficiency anemia. Peripheral blood smear demonstrated hypochromic microcytic anemia and thrombocytopenia with giant platelets. Laboratory investigations are shown in Table 1. Thyroid ultrasonography showed a nonspecific, enlarged, heterogeneous thyroid without increased vascularity. Nuclear medicine thyroid scan showed elevated thyroid uptake consistent with a diagnosis of Graves's disease. The differential diagnosis was secondary ITP with Grave's disease, methimazole-induced thrombocytopenia, or agranulocytosis. Methimazole was discontinued since admission, and methylprednisolone 1 mg/kg was started for suspected Grave's disease-induced secondary ITP, given her positive antiplatelet antibody. However, her platelet count remained low without significant response after 4 days of treatment. Hematology was consulted for further evaluation of other causes of thrombocytopenia. She underwent a bone marrow biopsy, revealing normocellular marrow with erythroid and megakaryocytic hyperplasia. Fluorescein-labeled proaerolysin (FLAER) was negative for paroxysmal nocturnal hemoglobinuria (PNH), and ADAMTS13 activity was within normal limits. Rheumatology was also consulted for further autoimmune workup due to a positive antineutrophil antibody (ANA) titer of 1:320 with a cytoplasmic, reticular pattern, positive anti-Sjogren's syndrome-related antigen A (SS-A) antibody, and family history of SLE. However, her clinical presentation was not consistent with any rheumatological autoimmune disorders. At this point, all investigations pointed toward the diagnosis of ITP secondary to Grave's disease. She was planned to restart MMI but refused due to its side effects. She opted to proceed with outpatient thyroid ablation with a closed follow-up on her platelet count and any signs of bleeding. At the time of her discharge on Day 10, her platelet count remained stable at 21,000/uL. She underwent outpatient radioactive ablation which was complicated by hyperthyroidism and required hospital admission due to her underlying pulmonary hypertension. She was treated with propylthiouracil (PTU), steroids, and oral cholestyramine. Her clinical continued to improve, and she was discharged eventually. On her recent follow-up visit, her platelet count returned to her baseline at 55,000/μL the 1 month after ablation (Figure 1 showing her platelet count trend).

3 | DISCUSSION

ITP is an acquired thrombocytopenia caused by autoantibodies against platelet antigens that accelerate platelet destruction and inhibit their production. The incidence of ITP is estimated to be 2 to 5 per 100,000 persons in the general population, which increases with age and has a slight female preponderance.[1] The diagnosis of ITP is categorized as primary or idiopathic, without identifiable cause, and secondary due to coexisting conditions, including infections, medications, or rheumatologic diseases. A secondary ITP has been concurrently reported with autoimmune thyroid disorders, including Graves's disease and Hashimoto's thyroiditis on several occasions with variable onset and clinical course. It can occur simultaneously during flares or even during the treatment of one of the comorbidities.[3] In a retrospective cohort

TABLE 1 Laboratory investigations during hospitalization.

	1 week prior	At admission	Normal range
Hemoglobin (g/dL)	10.1	9.8	11.2–15.7
Hematocrit (%)	33	30.1	44.1–44.9
MCV (fl)		78.1	79.4–94.8
WBC (K/μL)	5.28	6.24	3.98–10.04
Platelet (K/μL)	42	13	182–369
Thyroid-stimulating hormone (TSH) (mcIntUnit/mL)	<0.01	<0.01	0.27–4.2
Free T4 (ng/dL)	2.94	2.47	0.93–1.7
Free T3 (pg/mL)		4.58	2.3–4.2
Thyroid-stimulating immunoglobulin (TSI) (%baseline)		346	<140
TSH receptor Ab (IntUnits/L)		3.13	<2.00
Antithyroid peroxidase (anti-TPO) (IntUnits/mL)		>600	<34
Direct antiplatelet antibody		Positive	
Iron level (μg/dL)		17	37–145
TIBC (μg/dL)		346	250–450
Transferrin saturation (%)		8	5–62
Ferritin (ng/mL)		9.8	13–150
Transferrin (mg/dL)		300	200–360
HIV screen		Negative	
Hepatitis B and C		Negative	
Direct coombs		Negative	
Respiratory viral panel		Negatives	
C3 level (mg/dL)		124	90–180
C4 level (mg/dL)		14	10–40
ANA		1:320 with cytoplasmic, reticular pattern	
SS-A antibody		Positive with 5.00	0.2–1.0
Ds DNA, anti-ribosomal P, chromatin Ab, anti-smith, SS-B antibody, Scl 70 Ab, JO-1 Ab, anticentromere Ab, Anti Sn/RNP Ab		Negative	
Fluorescein-labeled proaerolysin (FLAER)		Negative	
ADAMTS13 activity (IntUnits/mL)		1.37	0.68–1.63
Peripheral blood smear		Hypochromic microcytic anemia and thrombocytopenia with giant platelets	

study, 64 out of 943 adult patients with ITP (6.79%) had hyperthyroidism, 25 out of 943 (2.65%) had hypothyroidism, and 107 of 943 (11.35%) had thyroid diseases. Those who had hyperthyroidism, hypothyroidism, and simple and unspecified goiter had higher odds of developing ITP, while thyroiditis and nontoxic nodular goiter do not show significantly increased risks of ITP.[2] In addition, previous studies demonstrated that antithyroid peroxidase (TPO) antibody and anti-thyroglobulin (anti-TG) were found in 30% and 10–40% of patients with ITP, respectively. While platelet-associated immunoglobulin G (PAIgG) levels were observed to be higher in patients with thyroid diseases, especially in Grave's disease but insignificant.[3,4]

The proposed mechanism is a cross-reaction between the antibodies' antithyroid receptors and the platelet epitopes, which could explain the association of both conditions. This hypothesis was strengthened by the structural similarity of the platelet membrane glycoprotein GPIDα and the TABP (truncated actin-binding protein), which is the binding protein to antithyroid antibodies. This suggests that the same antithyroid

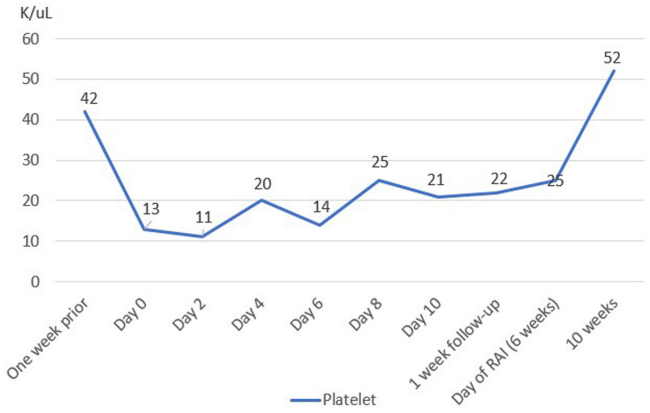

FIGURE 1 Trend of platelet count and timing during clinical course.

antibodies may react with platelet receptors by providing their early destruction. There is also some evidence of genetic predisposition related to human leukocyte antigen (HLA) B8 and DR3 in the coexistence of thyroid disorder and ITP.[3]

Pulmonary arterial hypertension is often reported to be complicated by thrombocytopenia due to several reasons and it can be found in up to 36% of IPAH populations.[5] Some possible mechanisms for IPAH and thrombocytopenia are blood flow through the pulmonary vasculature in presence of PH can lead to activation of thrombin inducing to platelet degranulation and aggregation, decreased in nitric oxide and soluble guanylyl cyclase production inducing platelet activation and aggregation, drug-induced thrombocytopenia or even ITP-induced thrombocytopenia.[6] One study reported ITP-induced thrombocytopenia in some cases with PAH for which many alternatives treatment including oral prednisolone, intravenous immunoglobulin, or splenectomy were found to yield unsatisfactory results.[7]

In our case, it is complicated as she has a history of and history of idiopathic pulmonary hypertension and baseline chronic thrombocytopenia due to Ambrisentan. It is a known adverse event of endothelin receptor antagonists according to meta-analysis.[8] However, this patient developed a sudden drop in her platelet count after being recently diagnosed with Graves's disease and started on antithyroid medication. All investigations, including positive antiplatelet antibody, giant platelet on the peripheral blood smear, and increased megakaryocytes from bone marrow biopsy pointed toward the diagnosis of ITP secondary to Grave's disease. American Society of Hematology (ASH) 2019 guidelines recommends treating newly diagnosed ITP in adults with a platelet of <30,000/μL in the absence of bleeding with corticosteroids.[1,9] Standard adult dosing is prednisone 0.5–2.0 mg/kg per day in a short course, including tapering (<6 weeks) or dexamethasone 40 mg per day for 4 days which both showed moderate response rates of 55% at 7 days and usually normalized within a month. Unless there is a contraindication of corticosteroids or a need for a more rapid response, intravenous immunoglobulin (IVIG) and anti-D immunoglobulin can be indicated.[1] However, several cases of ITP with thyroid disease have been observed to be refractory to corticosteroid treatment but have reported improvement or even resolution of refractory thrombocytopenia by treatment of underlying thyroid disorder like our case.[10] Nonetheless, the effect of thyroid disease and its treatment on ITP remains controversial.[11] In a review of cases on hyperthyroidism associated with ITP, it was estimated that 7% of the cases of ITP would respond to the treatment of the thyrotoxicosis, and that in many cases the thrombocytopenia would be resistant to other therapies.[3]

4 | CONCLUSIONS

This case highlights ITP in the settings of autoimmune thyroid diseases and pulmonary hypertension. Clinicians should be aware of the possible association between ITP and other diseases including autoimmune thyroid disorders when acute drop in platelet count occurs. This should be further investigated in future study for evaluation of ITP in setting of comorbidities that would affect platelet count namely pulmonary hypertension. Corticosteroids are the first line of primary and secondary ITP. Several reports indicate that ITP related to thyroid diseases can resolve with proper control of the underlying thyroid disease for which treatment should be cautiously considered to avoid adverse events from other coexisting diseases.

AUTHOR CONTRIBUTIONS

Pitchaporn Yingchoncharoen: Writing – original draft. **Mahmoud Abdelnabi:** Supervision; writing – review and editing. **Jerapas Thongpiya:** Writing – original draft. **Alexandra Hoffman:** Writing – original draft. **Hira Tariq:** Writing – original draft. **Neha Mittal:** Investigation; supervision; writing – review and editing.

CONFLICT OF INTEREST STATEMENT

All the authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

All data underlying the results are available as part of the article and no additional source data are required.

CONSENT

Verbal and written consent was obtained from She to publish her case.

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REFERENCES

1. Neunert C, Terrell DR, Arnold DM, et al. American Society of Hematology 2019 guidelines for immune thrombocytopenia. *Blood Adv*. 2019;3(23):3829-3866. doi:10.1182/bloodadvances.2019000966
2. Wu S-R, Kuo H-C, Huang W-C, et al. Incidence, clinical characteristics, and associated diseases in patients with immune thrombocytopenia: a nationwide population-based study in Taiwan. *Thromb Res*. 2018;164:90-95. doi:10.1016/j.thromres.2018.02.146
3. Marta GN, de Campos FP. Immune thrombocytopenia and autoimmune thyroid disease: a controversial overlap. *Autops Case Rep*. 2015;5(2):45-48. doi:10.4322/acr.2015.002
4. Ito S, Fujiwara S-i, Murahashi R, et al. Clinical association between thyroid disease and immune thrombocytopenia. *Ann Hematol*. 2021;100(2):345-352. doi:10.1007/s00277-020-04343-5
5. Thrombocytopenia In Idiopathic Pulmonary Arterial Hypertension. A58 Clinical Evaluation of Pulmonary Hypertension. A1883.
6. Kobayashi T, Shigeta A, Terada J, et al. Severe thrombocytopenia in patients with idiopathic pulmonary arterial hypertension provided several strategies for lung transplantation. *Pulm Circ*. 2020;10(4):2045894020969103. doi:10.1177/2045894020969103
7. Robbins IM, Gaine SP, Schilz R, Tapson VF, Rubin LJ, Loyd JE. Epoprostenol for treatment of pulmonary hypertension in patients with systemic lupus erythematosus. *Chest*. 2000;117(1):14-18. doi:10.1378/chest.117.1.14
8. Wei A, Gu Z, Li J, et al. Clinical adverse effects of endothelin receptor antagonists: insights from the meta-analysis of 4894 patients from 24 randomized double-blind placebo-controlled clinical trials. *J Am Heart Assoc*. 2016;5(11):1-25. doi:10.1161/jaha.116.003896
9. Kochhar M, Neunert C. Immune thrombocytopenia: a review of upfront treatment strategies. *Blood Rev*. 2021;49:100822. doi:10.1016/j.blre.2021.100822
10. Sugimoto K, Sasaki M, Isobe Y, Tamayose K, Hieda M, Oshimi K. Improvement of idiopathic thrombocytopenic purpura by antithyroid therapy. *Eur J Haematol*. 2005;74(1):73-74. doi:10.1111/j.1600-0609.2004.00341.x
11. Cheung E, Liebman HA. Thyroid disease in patients with immune thrombocytopenia. *Hematol Oncol Clin North Am*. 2009;23(6):1251-1260. doi:10.1016/j.hoc.2009.08.003

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