American Journal of Medical Case Reports, 2020, Vol. 8, No. 1, 14-17
Available online at http://pubs.sciepub.com/ajmcr/8/1/4
Published by Science and Education Publishing
DOI:10.12691/ajmcr-8-1-4

Thrombocytopenia in a Patient with Graves' Disease: An Uncommon Association of Two Common Autoimmune Diseases

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Received September 23, 2019; Revised November 02, 2019; Accepted November 18, 2019

Abstract We describe a 65-year-old male of Graves' disease with thyroid-associated orbitopathy who developed thrombocytopenia during the course of illness. Clinical features, temporal relationship with drugs and investigations supported the diagnosis of immune thrombocytoenic purpura. Several immunosuppressive drugs failed to improve thrombocytopenia. At last platelet count returned back to normal and remained stable with addition of dapsone and restoration of euthyroidism.

Keywords: *graves' disease, thrombocytopenia, immune thrombocytopenic purpura*

Cite This Article: Shahed-Morshed, Hasanat MA, Fariduddin Md, Nusrat-Sultana, Mahmood T, Ghani MH, Faisal I, and Sharmin-Jahan, "Thrombocytopenia in a Patient with Graves' Disease: An Uncommon Association of Two Common Autoimmune Diseases." *American Journal of Medical Case Reports*, vol. 8, no. 1 (2020): 14-17. doi: 10.12691/ajmcr-8-1-4.

1. Introduction

Graves' disease (GD) may affect hematological parameters in a small number of patients that are mostly clinically insignificant. Similarly, thrombocytopenia may develop in GD by several mechanisms. One of the mechanisms is peripheral destruction of platelets that is due to its autoimmune association with immune thrombocytopenic purpura (ITP) [1]. However the existence of these two diseases especially in a male is uncommon. Here, we describe a similar case report, review literature highlighting the mechanisms of thrombocytopenia in patients with GD and co-relate them with our patient.

2. Case Presentation

Our patient was diagnosed as a case of GD with inactive {clinical activity score (CAS)= 0/7} thyroid-associated orbitopathy (TAO) with hyperthyroidism status on the basis of clinical (toxic features, diffuse goiter without bruit, TAO) and biochemical (TSH <0.1 mIU/ml, FT4= 4.16 ng/dl) features. At that time his platelet count (PC) was normal (1,74,000/mm^3). He was treated with carbimazole (45 mg/ day) and propranolol. After 1 month, his clinical and biochemical features (FT_4= 2.14 ng/dl) of toxicosis improved but eye symptoms started to deteriorate (CAS= 2/7). 3 months later, the patient became hypothyroid (FT_4= 0.56 ng/dl, TSH= 13.26 mIU/ml) with further increase in TAO activity score (4/7). Carbimazole was stopped temporarily and he was advised for hospitalization to receive pulse methyl prednisolone (MP) therapy which was postponed due to presence of bilateral exposure keratitis. Meanwhile, the patient developed some ecchymoses and nonblanching purpuric spots over the abdomen (Figure 1) which were detected incidentally. Patient was otherwise normal without any fever, organomegaly, lymphadenopathy, bony tenderness, sore throat, oral ulcer or bleeding from other sites.

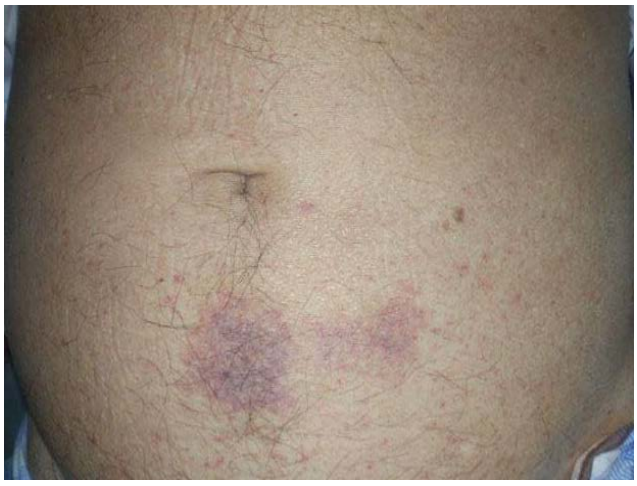

Figure 1. Purpura and ecchymoses in the abdomen of the patient

3. Investigations

A complete blood count (CBC) revealed PC= 5000/mm^3. Repeat CBC with peripheral blood film (Figure 2) was done to exclude pseudothrombocytopenia. However, the test again revealed more severe thrombocytopenia (1,000/mm^3). Other secondary causes of thrombocytopenia were excluded by appropriate investigations (Anti-HIVAb, HbsAg, Anti-HCVAb, ANA). Bone marrow examination was done to exclude any primary/ infiltrative marrow diseases which revealed megakaryocytic hyperplasia suggestive of immune thrombocytopenia (Figure 3). Other necessary investigations such as TSI, HLA and antiplatelet antibody could not be done due to their unavailability in our country.

4. Treatment

Initially two units aphretic platelets were given without any improvement of PC. After seeking consultation from haematologist, injection IV MP (1 gm daily for 5 days) was started considering the benefits of steroid treatment in this condition. This was followed by oral prednisolone. In spite of getting high dose of steroid, there was no significant improvement of PC. Even, 4 cycles of rituximab failed to improve PC to normal level. After excluding glucose-6-phosphate dehydrogenase deficiency, dapsone was started and PC came back to normal level. Meanwhile, patient again became thyrotoxic and carbimazole was started at low dose (20 mg/day). In the course of illness, patient became hypothyroid, again carbimazole was stopped and L-Thyroxine (50 µg/day) was started. The relationships among PC, FT4, drugs used to achieve euthyroidism and immunosuppression are shown in Figure 4.

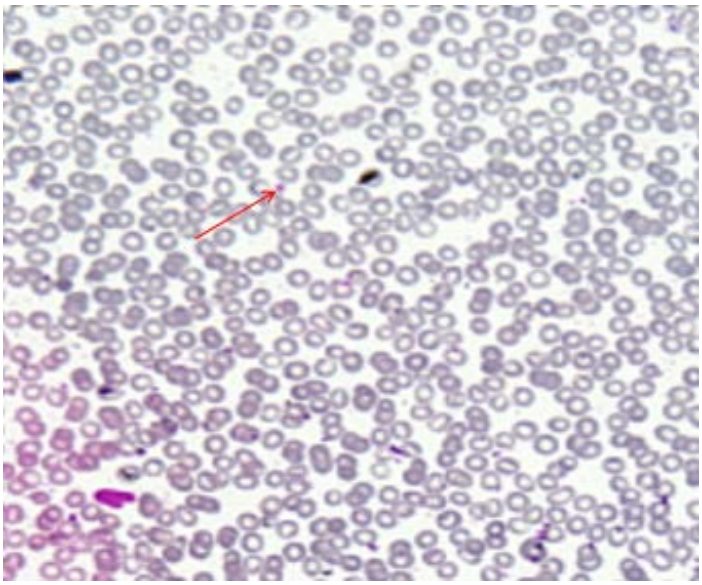

Figure 2. Paucity of platelets in peripheral blood film during diagnosis of thrombocytopenia (red arrow: platelet)

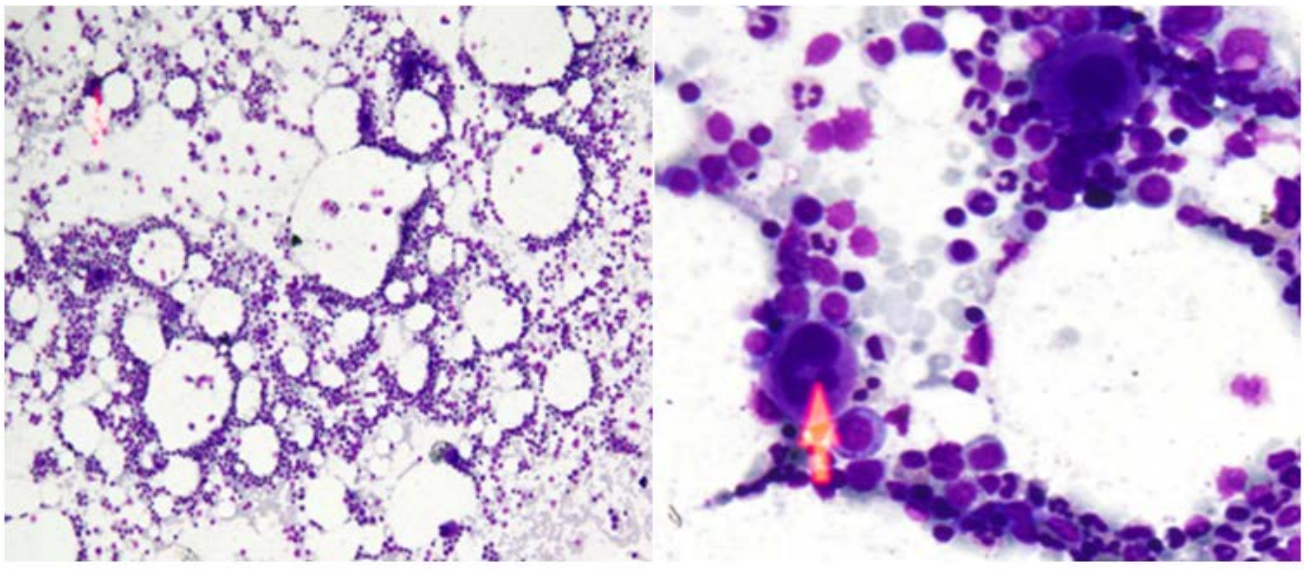

Figure 3. Bone marrow picture showing megakaryocytic hyperplasia (red arrow: Megakaryocyte)

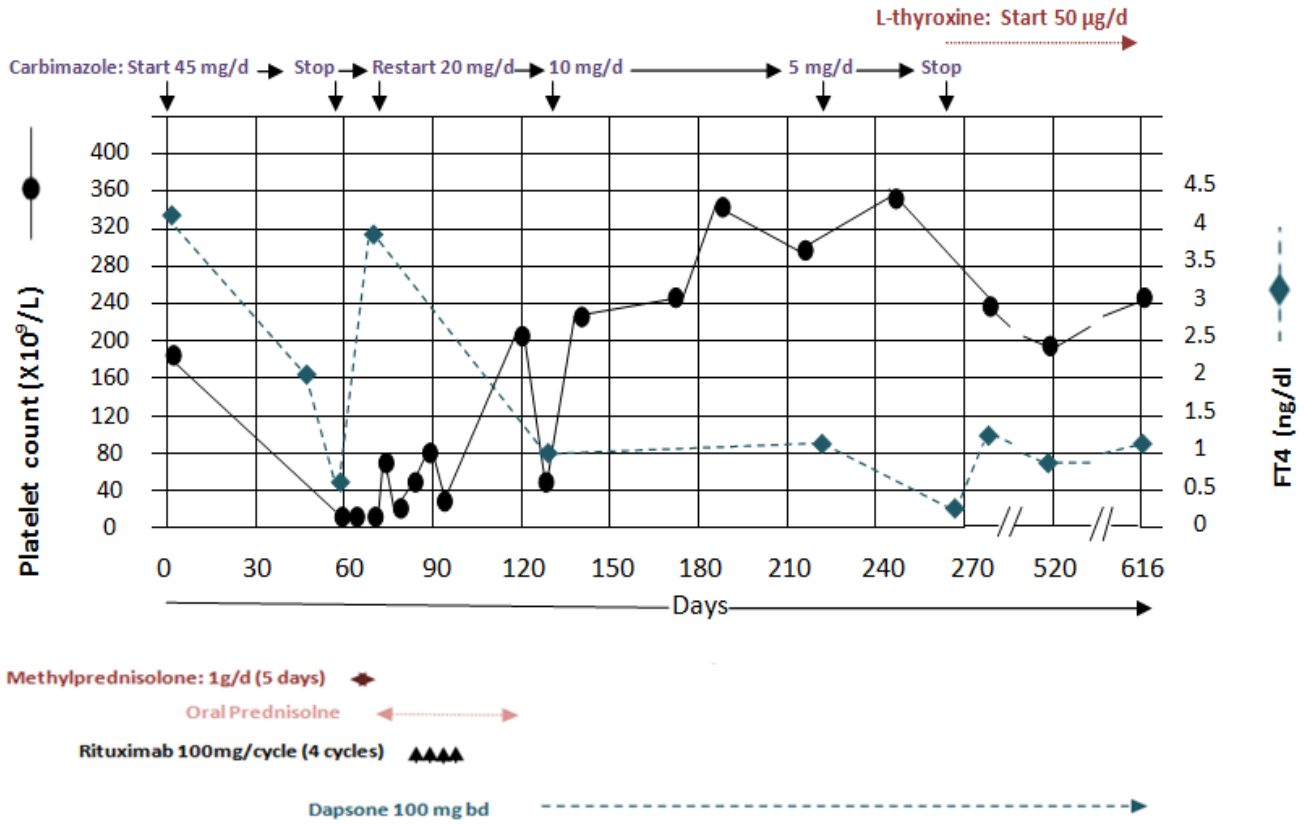

Figure 4. Platelet count and FT4 over time with drugs administered for treatment

5. Outcome and Follow-up

Approximately, during the 20 months course of illness, patient's PC became normal 7 days after starting dapsone and remained stable for the last 16 months of follow up period. The patient remained euthyroid for the last 11 months with L-Thyroxine. After the initiation of MP, patient's TAO remained inactive up to the last follow up.

6. Discussion

There are several proposed mechanisms of thrombocytopenia (Platelet count <1,50,000/ mm^3) in GD that include: thyrotoxicosis, molecular mimicry (ITP, Evan's syndrome) and drug-induced (such as thionamide) thrombocytopenia [2].

Thrombocytopenia due to thyrotoxicosis is usually mild (>1,00,000/ mm^3) and refractory to immunosuppressive treatment. Possible mechanisms of thyrotoxicosis-induced thrombocytopenia include thyrotoxicosis induced activation of reticuloendothelial system, increased clearance of platelets by spleen and alteration of platelets aggregation. Restoration of PC after reverting back to euthyroidism is the rule [3].

Another possibility of thrombocytopenia in patients' with GD is drug-induced (thionamides) platelet destruction. Drug induced thrombocytopenia usually develops 3 - 10 days after daily exposure, return to normal within 1 - 10 days of withdrawal [4]. However, isolated thrombocytopenia due to carbimazole is extremely rare; rather it develops as a part of pancytopenia [5]. In that case marrow hypoplasia is found in bone marrow examination and thrombocytopenia usually respond to platelet transfusion [4].

The autoimmune association between GD & ITP is well stated but the mechanism is not well described. Clustering of these two conditions in family members, genetic predisposition (presence of HLA B8, DR3, Bw35 antigen etc.) to autoimmunity and presence of related antibody of one disease in a person of another disease supports their autoimmune association [6]. Large platelet volume, low platelet distribution width and megakaryopoiesis in bone marrow also support the diagnosis. ITP may be both primary and secondary in GD. When the antithyroid antibodies (e.g., TSI and others) bind platelets and promote their destruction, this is called secondary ITP. This type of thrombocytopenia improves only after achieving euthyroidism by medical, surgical or radioablation means. It is refractory to immunosuppressive treatment that is described in most case reports, associating these two autoimmune diseases [7]. On the other hand, these two autoimmune conditions may be present in same person independently. Here, thrombocytopenia persists even after restoration of euthyroid status and require further immunosuppressive treatment. The period between the onset of clinically overt thyroid disease and immune ITP is variable [8]. This type of association is less commonly described than secondary ITP in the literature. Resnitzk et al described a 30 year female of thrombocytopenia with Graves' thyrotoxicosis which was initially managed by both prednisolone and antithyroid therapy. But she again developed thrombocytopenia after 2½ years when she was euthyroid. This time patient's PC improved after splenectomy with prednisolone [2]. Another case of autoimmune polyendocrinopathy (Type 1 diabetes

mellitus, Graves' disease and positive antiparietal cell antibody) who developed thrombocytopenia at her age of 39 years when she was euthyroid and also successfully managed by splenectomy [9]. Both of the above cases were female who developed thrombocytopenia clearly during euthyroid status and responded to prednisolone and ultimately by splenectomy. On the other hand, Aubert et al. described 2 cases that developed thrombocytopenia during thyrotoxic state but did not improve even after achievement of euthyroid status [10].

The low PC and hypothyroid status during the development of thrombocytopenia in our patient does not support thyrotoxicosis as a cause of thrombocytopenia. Our patient developed thrombocytopenia 5 days after withdrawal of carbimazole therapy and he was hypothyroid at that time. Again there was no deterioration of PC when we restarted the drug during thyrotoxic state. Nonresponsive to platelet transfusion, absence of other cell-line involvement and marrow hyperplasia further support that drug is not the responsible factor in this case. As other secondary causes of thrombocytopenia were also excluded, probably, he was a case of immune thrombocytopenia either primary or secondary. Our patient was relatively an older male who developed thrombocytopenia during the treatment period and did not improve with corticosteroid and rituximab but later responded to dapsone when thyrotoxic status also subsided. Dapsone is an effective (overall response rate: 58.4%) 2nd line treatment of ITP with good safety profile at a low cost [11]. However, use of dapsone in thrombocytopenia with GD is rarely described in the literature. Jung et al. described a 24-year-female of ITP with thyrotoxicosis who did not respond to dapsone, later improved after achievement of euthyroid status by radioiodine therapy [12]. So in our case, sustained normalization of PC whether due to resolution of thyrotoxicosis or to dapsone could not be concluded.

Funding Statement

We did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sector.

Declaration of Interest

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Patient Consent

Patient's consent has been obtained for the publication of this case report.

Authors' Contributions and Acknowledgements

Shahed Morshed was responsible for writing the manuscript, researching the discussion, and follow up of the patient; Tahseen Mahmood, Habibul Ghani and Ibrahim Faisal were responsible for data & image collectoin and treatment of the patient; Sharmin Jahan and Nusrat Sultana were the senior authors and were responsible for supervision, obtaining patient's consent, and reviewing and editing the final manuscript. MA Hasanat & Md. Farid Uddin were were responsible for overall management of the patient.

We acknowledge the contribution of Department of Haematology and Ophthalmology of Bangabandhu Sheikh Mujib Medical University for their valuable opinion in patient management.

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