



CYCLICAL THROMBOCYTOPENIA: A DIAGNOSTIC DILEMMA

Haematology

Balachandra Routhu	MBBS, Junior Resident, Department Of Medicine, All India Institute Of Medical Sciences, Rishikesh
Rifika Bansal*	MBBS, MD, Senior Resident, Department Of Medicine, All India Institute Of Medical Sciences, Rishikesh *Corresponding Author
Ajinkya Rahatgaonkar	MBBS, MD, Junior Resident, Department Of Medicine, All India Institute Of Medical Sciences, Rishikesh
Santhosh SC	MBBS, MD, Department Of Medicine, Junior Resident, All India Institute Of Medical Sciences, Rishikesh
Om Sharma	MBBS, Junior Resident, Department Of Medicine, All India Institute Of Medical Sciences, Rishikesh
Sukdev Manna	MBBS, MD, DM, Assistant Professor, Department Of Medicine, All India Institute Of Medical Sciences, Kalyani
Ravi Kant	MBBS, MD, Professor And Head, Department Of Medicine, All India Institute Of Medical Sciences, Rishikesh

ABSTRACT

Cyclical thrombocytopenia (CTP) is a rare hematological disorder that is defined by period fluctuations in platelet counts, leading to symptomatic thrombocytopenia. It is frequently misdiagnosed as immune thrombocytopenic purpura (ITP) and poses a unique diagnostic and therapeutic challenge to physicians. Its pathophysiology is still elusive, and its clinical course is unpredictable. We report the case of a 45-year-old female who presented with multiple episodes of mucocutaneous bleeding and thrombocytopenia and was initially managed as ITP, which proved to be ineffective. A review of her medical history was suggestive of recurrent episodes of symptomatic thrombocytopenia, and corresponding serial platelet monitoring showed cyclical platelet fluctuations, subsequently leading to a diagnosis of CTP. This case highlights the importance of recognizing CTP as a distinct clinical entity and including it in the differential diagnosis while working up a patient with thrombocytopenia. Further research is warranted to illustrate its pathogenesis, develop novel therapeutic options, and improve patient outcomes.

KEYWORDS

Thrombocytopenia, Cyclical thrombocytopenia, Immune thrombocytopenic purpura

INTRODUCTION

Thrombocytopenia is defined as a subnormal number of platelets in the circulating blood.[1] It has a wide variety of etiologies. Cyclical thrombocytopenia (CTP) is a rare hematological entity characterized by periodic oscillations in platelet counts. With less than a hundred reported cases, cyclical thrombocytopenia remains a diagnostic challenge and is often misdiagnosed and treated as primary immune thrombocytopenic purpura (ITP)[2]. Although several pathophysiological mechanisms have been proposed, its pathophysiology is not entirely understood. The clinical phenotype is usually mild, with patients presenting with mucocutaneous bleeding manifestations, including petechiae, epistaxis, and genitourinary bleeding [3]. Diagnosis is usually made by frequent platelet monitoring over time. Patients are usually subjected to ITP-specific therapies, including steroids, thrombopoietin receptor agonists, rituximab, and splenectomy – often with a suboptimal response. Danazol and cyclosporine A have also been tried as therapies for cyclical thrombocytopenia [4]. We report the case of a 45-year-old female who presented with multiple episodes of symptomatic thrombocytopenia and was initially managed as ITP, only to be later re-diagnosed as cyclical thrombocytopenia.

CASE SUMMARY

Our patient is a 45-year-old female with significant past medical history of type 2 diabetes mellitus and hypertension. She also had a past surgical history of hysterectomy (for uterine fibroids), left cortical mastoidectomy (for left chronic suppurative otitis media), and bilateral eye cataract surgeries. She presented to the outpatient department of our hospital with complaints of epistaxis and bleeding from gums and left ear for one day, preceded by an episode of shivering lasting for around 20 minutes, which resolved spontaneously. There were no complaints of fever, cough, loose stools, pain abdomen, loss of consciousness, melæna, hematemesis, hematuria or any other bleeding manifestations. On physical examination, she had petechiae on both her upper limbs and the front of her torso. Petechial spots were seen in her oral cavity as well. There was no lymphadenopathy or hepatosplenomegaly. Local ear and nose examination did not reveal

any contributory local pathologies. Laboratory investigations revealed a platelet count of $8 \times 10^3/\mu\text{L}$ (Range: 150-450/ $10^3/\mu\text{L}$), a total leukocyte count of $6.72 \times 10^3/\mu\text{L}$ (Range: 4-11 $10^3/\mu\text{L}$), and a hemoglobin of 10.3g/dL (Range: 12-15g/dL). Peripheral blood smear showed microcytic hypochromic red cells, normal counts and distribution of white blood cells, and markedly reduced platelets without any evidence of platelet clumping. There was no evidence of any schistocytes, dyserythropoiesis, or abnormal cells. An ultrasonography of the abdomen did not reveal any significant abnormality. The patient was worked up for the cause of thrombocytopenia. A manual platelet count was done to confirm the same initially. Tests for HBsAg, anti-HCV, and anti-HIV antibodies were non-reactive. Evaluation for anemia was suggestive of iron deficiency with normal serum vitamin B12 and folate levels. Direct and Indirect Coombs' tests were negative. LDH and bilirubin levels were within normal limits. Bone marrow aspiration showed a cellular marrow with normal megakaryopoiesis. The patient was euthyroid. ANA by IFA was also negative.

The patient was given platelet transfusions, following which her bleeding stopped. Upon further investigation, the patient reported a history of similar episodes in the past – a total of 4 episodes over the past year wherein she would develop symptomatic thrombocytopenia preceded by an episode of chills. She was hospitalized at all these incidents and was managed conservatively with a transfusion of platelets. At all episodes, the patient's platelet counts returned to normal without receiving any targeted therapy in the form of steroids, IVIg, or thrombopoietic agents.

A hematology consult was taken. Initially, a diagnosis of primary ITP was made, and the patient was started on eltrombopag therapy. As her platelets were on an improving trend ($123 \times 10^3/\mu\text{L}$ at discharge), she was discharged with advice to follow up in the outpatient department.

Three days later, the patient presented to the emergency department with complaints of epistaxis and bleeding from her left ear. This was preceded by an episode of chills. On examination, she had multiple

petechiae over her body, and laboratory investigations revealed a platelet count of $3 \times 10^3/\mu\text{L}$. She was re-admitted and received platelet transfusions. Her platelet count was serially monitored daily, and it showed rapid improvement to more than $200 \times 10^3/\mu\text{L}$.

Considering her pattern of fluctuating platelet counts with spontaneous improvement, the patient was, hence, diagnosed with cyclical thrombocytopenia.

Table 1. Platelet count

Date	9/11/23	10/1/23	18/1/23	19/12/23	20/1/23	21/1/23	22/1/23	23/12/23	
PLT COUNT ($\times 10^3/\text{cumm}$)	148	141	21	24	22	50	75	109	
DATE	3/1/24	5/1/24	7/1/24	8/1/24	13/1/24	14/1/24	15/1/24	16/1/24	17/1/24
PLT COUNT ($\times 10^3/\text{cumm}$)	8	45	86	123	3	36	74	155	214

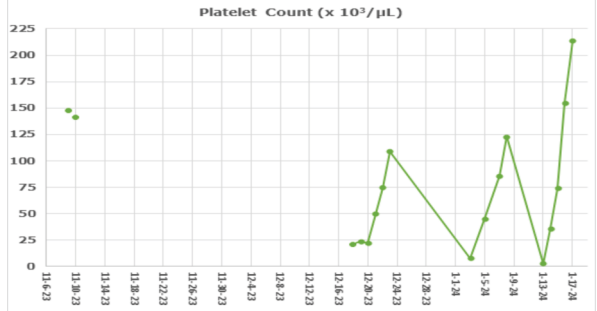


Figure 1. Platelet count

DISCUSSION

Cyclical thrombocytopenia is a rare entity that is distinguished by fluctuating platelet counts. Thrombocytopenia is often symptomatic, leading to mucocutaneous bleeding and, rarely, intracranial hemorrhage.[3] Previous literature suggests that it is often misdiagnosed as ITP and treated as such initially, thus exposing the patients to unnecessary therapies, which often do not lead to a satisfactory response. Our patient also presented with symptoms of mucocutaneous bleeding.

The pathogenesis of CTP has yet to be entirely understood. Multiple mechanisms have been proposed, including:[2]

1. Autoimmune-mediated platelet destruction
2. Megakaryocyte hypoplasia
3. T-cell receptor rearrangement
4. Abnormal regulation of platelet production
5. Synchronization with the menstrual cycle [5]
6. Associated with thyroid gland disorders
7. Associated with hematological malignancies
8. Associated with cyclical neutropenia

To understand the biology behind it, Apostu et al. [6] proposed a mathematical model based on published data that simulates the characteristics of cyclical thrombocytopenia and provides insights into its biology.

Owing to its presentation similar to acute ITP, cyclical thrombocytopenia often remains undiagnosed for years. According to a study by Steinbrecher et al. [4], the time interval between the diagnosis of ITP and CTP can range between three months to ten years. In our case, the time from the first episode to the diagnosis of cyclical thrombocytopenia was about 7 months.

CTP presents more frequently in women, often young premenopausal women, although it may also occur in men and postmenopausal women, as was seen in our case.

The diagnosis of CTP requires a high degree of suspicion. Serial platelet monitoring must be done without any pharmacological treatment, which will demonstrate the periodicity of this disease. Apart from being a diagnostic challenge, CTP is also a therapeutic challenge. Currently, there are no protocols or designated therapies available for cyclical thrombocytopenia. Most patients usually receive ITP-specific treatments, including corticosteroids, thrombopoietin receptor agonists, rituximab, or splenectomy. Some patients respond to danazol

or cyclosporine. However, response to these agents is usually suboptimal – there may be an initial improvement in platelet count which is incorrectly attributed to the therapy as inevitably, there is a recurrence of thrombocytopenia, which is incorrectly labelled as treatment failure. Long-term outcomes are unknown in these patients and require more studies, although spontaneous remission has been reported in some patients, even after years.

In our case, the patient's thrombocytopenia initially improved after receiving eltrombopag therapy. However, there was a relapse just a few days which was managed with platelet transfusions only. A review of her records and serial platelet count monitoring over a period of time demonstrated the fluctuating counts of her platelet count leading to a diagnosis of cyclical thrombocytopenia.

CONCLUSION

Cyclical thrombocytopenia (CTP) is a disease with a yet unknown pathophysiology, which usually causes mild mucocutaneous bleeding. Its presentation is similar to primary ITP and is often diagnosed and treated as such, only to be later diagnosed as CTP. Diagnosis requires a high level of suspicion by the treating physician and is vital for early diagnosis to reduce patient exposure to unnecessary treatment. To our knowledge, no such case has been reported in India. More research is needed to fully understand the pathogenesis of the disease, provide better therapeutic options to the patients, and improve outcomes in such patients.

REFERENCES

1. Greer, J. P., Arber, D. A., Glader, B., List, A. F., Means, R. T., Paraskevas, F., & Rodgers, G. M. (2013). *Wintrobe's Clinical Hematology*. Wolters Kluwer Health. <https://books.google.co.in/books?id=NYCeAgAAQBAJ>
2. Kyrle, P. A., & Eichinger, S. (2021). How I manage cyclic thrombocytopenia. *Blood*, 137(2), 178-184. <https://doi.org/10.1182/blood.2020008218>
3. Balduini, C. L., Stella, C. C., Rosti, V., Bertolino, G., Noris, P., & Ascari, E. (1993). Acquired cyclic thrombocytopenia thrombocytosis with periodic defect of platelet function. *British Journal of Haematology*, 85.
4. Steinbrecher, O., Mitrovic, M., Eischer, L., Sinkovec, H., Eichinger, S., & Kyrle, P. A. (2020). Clinical and laboratory characteristics of cyclic thrombocytopenia: an observational study. *Haematologica*, 105(4), e198-e201. <https://doi.org/10.3324/haematol.2019.237909>
5. Menakuru, S. R., Priscu, A., Dhillon, V., & Salih, A. (2022). Cyclical Thrombocytopenia Synchronized With the Patient's Menstrual Cycle Treated With Danazol [Cyclical thrombocytopenia; Immune thrombocytopenia; Danazol]. <https://www.thejh.org/index.php/jh/article/view/964/628>
6. Apostu, R., & Mackey, M. C. (2008). Understanding cyclical thrombocytopenia: a mathematical modeling approach. *J Theor Biol*, 251(2), 297-316. <https://doi.org/10.1016/j.jtbi.2007.11.029>