CYCLIC THROMBOCYTOPENIA TREATED WITH PLATELET TRANSFUSION AND ORAL PREPARATION CONTAINING HYALURONIC ACID (ORALVISC®)

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Short Title: A case of cyclic thrombocytopenia

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KEY CLINICAL MESSAGE

Cyclic thrombocytopenia is a rare disorder characterized by periodic platelet fluctuation with amplitude from low to high. There are no standardized treatment guidelines. We present a patient who had resolution of mucocutaneous bleeding with platelet transfusion at platelet nadir, normalization of platelets with an oral preparation containing hyaluronic acid (Oralvisc®).

INTRODUCTION

Cyclic thrombocytopenia (CTP) is a rare disorder characterized by intense fluctuations of platelet counts in a cyclical pattern repeating on an average of a 3-week basis.[1] Platelet nadir can be complicated by hemorrhage, and thrombocytosis can cause hypercoagulable state and thrombosis. Initially, most CTP patients are typically misdiagnosed as having primary immune thrombocytopenia (ITP). Currently it is considered

to be heterogenous in cause. Clinical presentation is similar to immune thrombocytopenia (ITP), however most treatments seem to be ineffective or even harmful if applied to patients with CTP. CTP is a diagnosis of exclusion and is usually established, if at all, much later, often at a time when ITP-specific therapies have failed. Due to its rarity, in addition to the lack of research and documentation surrounding it there are no standardized guidelines on treatment. Here we present a case of chronic CTP, who reached significant improvement in quality of life after initiation of supportive platelet transfusions at platelet nadir. Moreover, platelet count fluctuations decreased and eventually normalized after application of oral preparation containing hyaluronic acid (Oralvisc®) for concomitant arthropathy. With this case we want to illustrate challenging aspects of non-standard management for such a rare disease.

CASE HISTORY / EXAMINATION

64-year-old female was referred to our institution for management of chronic CTP. She was diagnosed at the age of 45, initially as ITP, when routine blood work was performed prior to minor surgery. Past medical history included calcium pyrophosphate deposition disease (CPPD), hypertension, hearing impairment, myopia, peripheral neuropathy, atrial fibrillation, chronic back pain, cholecystectomy, and excised squamous cell carcinoma on floor of mouth. There was no history of alcohol or substance abuse. She had 20 pack year history of smoking, quit one year before CTP diagnosis. Family history was unremarkable. Platelet fluctuations were not synchronized with patient's menstrual cycle. At the time of initial assessment at our institution her platelet count fluctuated from mild thrombocytosis (˜600,000 x 10^9/L) to severe thrombocytopenia (5,000 x 10^9/L) as shown in Figure 1. Bone marrow examination at diagnosis did not reveal myelodysplastic changes, abnormal lymphoid or plasma cell population. There was mild megakaryocytic hypoplasia. At the time of diagnosis, she was asymptomatic, but after 12 months started developing muco-cutaneous bleeding around nadir time of the platelet. She has no major bleeding, including hemarthroses, hematuria, hematoschezia.

METHODS (TREATMENT)

Given CHADS2 score of 1 at diagnosis of atrial fibrillation, she was anticoagulated with warfarin. However, due to bleeding episodes it was switched to low molecular dose heparin, and later to apixaban. That allowed a better balance of bleeding and thrombosis risks during thrombocytopenia and thrombocytosis.

After taking Prednisone 1 mg/kg she achieved partial response but discontinued it due to recurrent mouth thrush. She switched to a pulse dose of dexamethasone; however it was stopped because of vaginal pain and bleeding, and feeling generally unwell. She had normalization of platelet count on oral cyclophosphamide 100 mg daily and was able to stop it. However, she relapsed shortly after discontinuation and had no significant clinical response following restarting of cyclophosphamide. Next line of therapy was course of intravenous infusion of Rituximab, 375 mg/m^2 weekly x4. There was no platelet improvement, but she developed significant daily headaches, visual hallucinations, and blue vision discoloration. She declined splenectomy and was on active surveillance until bleeding symptoms at her platelets nadir progressed and started significantly affect her quality of life . High doses of tranexamic acid (1,000mg three times a day) were given at platelet nadir to improve symptomatic bleeding, but the patient had only marginal improvement and it was discontinued. Due to risk of thrombosis at platelet high, we considered it unsafe to administer thrombopoietin receptor agonists, like eltrombopag or romiplostim.

OUTCOME

Due to lack of other options, we offered her platelet transfusion around nadir time which led to marked improvement in bleeding episodes. Since the timing of nadir was quite predictable, platelet transfusion improved quality of life. When the patient required dental extraction, we chose a time when the patient had a normal platelet count which resulted in an unremarkable procedure with no bleeding or thrombosis. After 2 years of platelet transfusion, the patient started taking oral preparation containing hyaluronic acid (Oralvisc®) for worsening hip and knee arthropathy. After five months her platelet count fluctuations improved, ranging from 100,000 to 150,000 x 10^9/L and she became transfusion independent. After 26 months the patient discontinued Oralvisc® due to supply issues and switched to colchicine. For over 19 months platelet count remains within the same range, and she remains asymptomatic and transfusion independent.

Her physical examination is unremarkable.

DISCUSSION

ITP or immune thrombocytopenia is a platelet disorder defined by a low platelet count thought to be a result of the immune system destroying platelets either alone or in conjunction with thrombopoeisis inhibition. Common symptoms include skin and mucocutaneous hemorrhage, bruising, fatigue. ITP is diagnosis of exclusion and requires an extensive work up to rule out secondary causes and other platelet disorders. Corticosteroids (prednisone or dexamethasone) are standard frontline therapy. Platelet transfusions are not usually effective, since there is rapid destruction of transfused platelets. For relapsed disease rituximab, steroid-sparing immunosuppressants, or splenectomy are used.

CTP is a similar platelet disorder however it is characterized by periods of low and high platelet counts in a reoccurring wave-like pattern every few weeks. Currently CTP is considered to be heterogenous in cause and the pathophysiology is largely unknown[1]. Germline heterozygous loss-of-function thrombopoietin receptor MPL mutation and pathogenic somatic gain-of-function (GOF) variants in signal transducer and activator of transcription 3 (STAT3) were shown in two patients with CTP. Interesting that 2 patients had also clonal T-cell populations. It was suggested that these mutations along with clonal T cells trigger exaggerated persistent thrombopoiesis oscillations of their intrinsic rhythm upon homeostatic perturbations[2].

Many patients are usually treated for ITP initially prior to diagnosis[3]. Two clinical features relatively unique to CTP besides periodic thrombocytopenia are rebound thrombocytosis unrelated to recent splenectomy and platelet nadirs occurring during menses[4]. To establish a proper diagnosis, platelet count needs to be measured every week over a period of 1-3 months to establish the presence of a cyclical pattern to diagnose CTP, however it is usually a diagnosis of exclusion. Currently it is considered to be heterogenous in cause.[1]

Due to rarity of disease and alternating thrombocytopenia and thrombocytosis the treatment options for CTP are limited. In addition to detailed medical history and physical examination to rule out secondary causes, in non-bleeding patients serial blood count check to establish the platelet profile is recommended. In a patient with active bleeding, platelet transfusion with post-transfusion blood count check would be beneficial to assess whether platelets are actively destroyed as seen in ITP or maintain the count, which would ne more suggestive as CTP. For asymptomatic patients active surveillance is recommended until they develop clinically significant and recurrent hemorrhage affecting organ function or quality of life. Patients with CTP generally do not respond to standard ITP treatments, including corticosteroids, splenectomy, and intravenous immunoglobulin[1,4]. A recent publication showed normalization of platelet count in a female patient treated with danazol[5]. Hormonal contraceptive showed efficacy in alleviating patient's symptoms[6].

Platelet transfusions in ITP patients are generally reserved for critical bleeding when there is a need to raise the platelet count immediately[7]. Due to antiplatelet antibodies that destroy circulating platelets and megakaryocytes in the bone marrow the response is transient and attenuated[8]. Based on our experience, supportive single platelet transfusion per cycle at the nadir of platelet is efficacious in long-term management of CTP. It helps to minimize bleeding and improve quality of life. Given predictable pattern of platelet count fluctuation, it is feasible to arrange blood count check and transfusions. Transfusion of platelets does not increase risk pf thrombosis. In contrast to ITP, there is not rapid platelet destruction in CTP patients and the longevity of transfused platelet is longer. This approach could also be used perioperatively prior to major or minor surgeries. The sustained response to platelet transfusion in CTP patient preoperatively was shown recently[9].

Efficacy of anti-inflammatory medications in ITP has not been shown. Oralvisc® is an anti-inflammatory oral preparation containing hyaluronic acid that reduces the levels of pro-inflammatory mediators leptin and bradykinin[10]. Bradykinin receptors exist in chondrocytes and on stimulation increase Interleukin-1. Bradykinins are known to participate in innate immunity, inflammation, and pain[11]. Hence, evidence of reduction in bradykinin levels is clinically relevant. Though prior to starting Oralvisc® the patient had no elevated markers of inflammation (C-reactive protein, erythrocyte sedimentation rate, fibrinogen and ferritin were normal), the anti-inflammatory effect may have contributed to normalization of platelet count and

clinical improvement. Alternatively, in our case Oralvisc® may triggered spontaneous recovery, a feature previously described in CTP[1].

CONCLUSION

CTP is a rare disease, different from ITP, however it should be considered at the initial presentation. In patients with recurrent fluctuation in their platelet count, CTP should be considered. Serial blood count check is recommended to establish a proper diagnosis and avoid unnecessary therapies used for ITP but not effective in CTP. Supportive platelet transfusion at the nadir of thrombocytopenia is an effective management option in some symptomatic patients. Anti-inflammatory medications, suppressing bradykinin and leptin may be applied to alleviate platelet fluctuation and improve symptoms.

AUTHOR CONTRIBUTIONS

Marek Benjamin: Writing – original draft; writing – review and editing. Rouslan Kotchetkov: Writing – review and editing, Supervision.

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CONFLICT OF INTEREST STATEMENT

None Declared.

CONSENT

Complete written informed consent was obtained from the patient for the publication of this study and accompanying images.

FIGURE LEGEND

Figure 1: Fluctuating platelet count/μL over a period of the last 5 years. Arrow represents the point at which the patient started Oralvisc®. Red line – lower limit of norm, grey line – upper limit of norm

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