Trombosis venosa cerebral: una etiología rara

Cerebral Venous Thrombosis – A Rare Etiology

Nuno Leal[1], António Campos[2], Pedro Barros[2], Miguel Veloso[2], José Ribeiro-Almeida[1], Sara Pinto[1]

[1] Serviço de Medicina Interna. Centro Hospitalar de Vila Nova De Gaia/Espinho. Vila Nova de Gaia (Portugal)
[2] Serviço de Neurologia. Centro Hospitalar de Vila Nova De Gaia/Espinho. Vila Nova de Gaia (Portugal)

ABSTRACT

Idiopathic thrombocytopenic purpura is an immune-mediated disease that courses with thrombocytopenia. Eltrombopag is a thrombopoietin receptor agonist used as a second-line treatment for this disease to increase platelet count. The association of this drug with thrombotic events is known, however, with few cases of venous sinus thrombosis described in the literature.

We present a 26-year-old female with idiopathic thrombocytopenic purpura diagnosed at the of age 14, splenectomized and previously treated with immunoglobulins, corticosteroids, and rituximab, with no response, who was started on oral estroprogestative and eltrombopag, with multiple dose increases, for 3 months. She was admitted to the emergency room with a 3-day history of severe frontal headache, with phono and photophobia, nausea, vomiting, and confusion. Physical examination was remarkable only for mild paraphasias, anomalous pauses, and difficulty in reading. Routine labs showed mild thrombocytopenia, leukocytosis, and elevated C-reactive Protein. She performed a brain computerized tomography and magnetic resonance that demonstrated extensive venous sinus thrombosis. She was admitted to the ward with eltrombopag suspension and enoxaparin 1mg/kg bid. Increasing thrombocytosis was observed for nine days, with a subsequent decrease to normal levels. Sequenced cerebral tomography showed hemorrhage reabsorption. At discharge, there was no improvement of neurological deficits and dabigatran 150mg bid was started for secondary prophylaxis.

Despite contradictory data relating specifically to eltrombopag, a thrombotic event following multiple dose increases was described before, and it makes the more likely culprit for this event. The treatment of venous sinus thrombosis is based on anticoagulants, and we chose dabigatran for the ease of use and the existence of a readily available antidote.

This association between eltrombopag and thrombosis means patients should be advised to avoid prothrombotic risk factors such as smoking, obesity, oral estroprogestative, and immobilization. Some common symptoms associated with this drug, like headache and nausea should always be taken seriously, since they can be also found in venous sinus thrombosis.

Keyword: cerebral venous thrombosis, eltrombopag, idiopathic thrombocytopenic purpura, thrombocytosis.

RESUMEN

La púrpura trombocitopénica idiopática es una enfermedad inmunomediada que cursa con trombocitopenia. Eltrombopag es un agonista del receptor de trombopoyetina que se utiliza como tratamiento de segunda línea de esta enfermedad para aumentar el recuento de plaquetas. Sin embargo, se conoce la asociación de este fármaco con acontecimientos trombóticos, con pocos casos de trombosis del seno venoso descritos en la literatura.

Presentamos el caso de una mujer de 26 años con púrpura trombocitopénica idiopática diagnosticada a los 14 años, esplenectomizada y tratada previamente con inmunoglobulinas, corticoides y rituximab, sin respuesta, a la que se inició tratamiento con estroprogestativos orales y eltrombopag, con múltiples incrementos de dosis, durante 3 meses. Ingresó en urgencias con un cuadro de 3 días de evolución de cefalea frontal intensa, con fono y fotofobia, náuseas, vómitos y confusión. En la exploración física sólo destacaban parafasias leves, pausas anómalas y dificultad para leer. Los análisis de rutina mostraron trombocitopenia leve, leucocitosis y proteína C reactiva elevada. Se le realizó una tomografía computarizada cerebral y una resonancia magnética que demostraron una extensa trombosis del seno venoso. Fue ingresada en planta con eltrombopag en suspensión y enoxaparina 1mg/kg bid. Se observó un aumento de la trombocitosis durante nueve días, con una disminución posterior a niveles normales. La tomografía cerebral secuenciada mostró reabsorción de la hemorragia. Al alta, no hubo mejoría de los déficits neurológicos y se inició dabigatrán 150mg bid para profilaxis secundaria.

A pesar de los datos contradictorios relativos específicamente al eltrombopag, ya se había descrito un acontecimiento trombótico tras múltiples aumentos de dosis, por lo que resulta el culpable más probable de este acontecimiento. El tratamiento de la trombosis del seno venoso se basa en los anticoagulantes, y elegimos el dabigatrán por la facilidad de uso y la existencia de un antídoto fácilmente disponible.

Esta asociación entre eltrombopag y trombosis significa que se debe aconsejar a los pacientes que eviten los factores de riesgo protrombóticos como el tabaquismo, la obesidad, los estroprogestativos orales y la inmovilización. Algunos síntomas comunes asociados a este fármaco, como el dolor de cabeza y las náuseas, deben tomarse siempre en serio, ya que también pueden aparecer en la trombosis del seno venoso.

Palabras clave: trombosis venosa cerebral, eltrombopag, púrpura trombocitopénica idiopática, trombocitosis.

INTRODUCTION

Idiopathic thrombocytopenic purpura (ITP), formerly known as idiopathic thrombocytopenic purpura, is an immune-mediated disease that courses with thrombocytopenia resulting from autoantibody-mediated, peripheral platelet destruction, and suboptimal platelet production.[1,2] With an incidence of 3.3/100,000/year, in adults it's usually a chronic disease, augmenting the risk of major bleeding events, bruising and *petechiae*.[2] The more life-threatening manifestation of this disease is intracranial hemorrhage, whose frequency is estimated to be around 1.4% in adults, and occurs especially when the platelet count is less than 10,000.[3] Despite the hemorrhagic risk, a link between primary immune thrombocytopenia in adults and thromboembolic events is increasingly acknowledged.[2]

The mainstay of treatment relies on the use of corticosteroids, immunoglobulins, and splenectomy, although rituximab may be considered for patients at high risk of bleeding who have failed one line of therapy.[4]

Correspondencia: nunofleal@gmail.com
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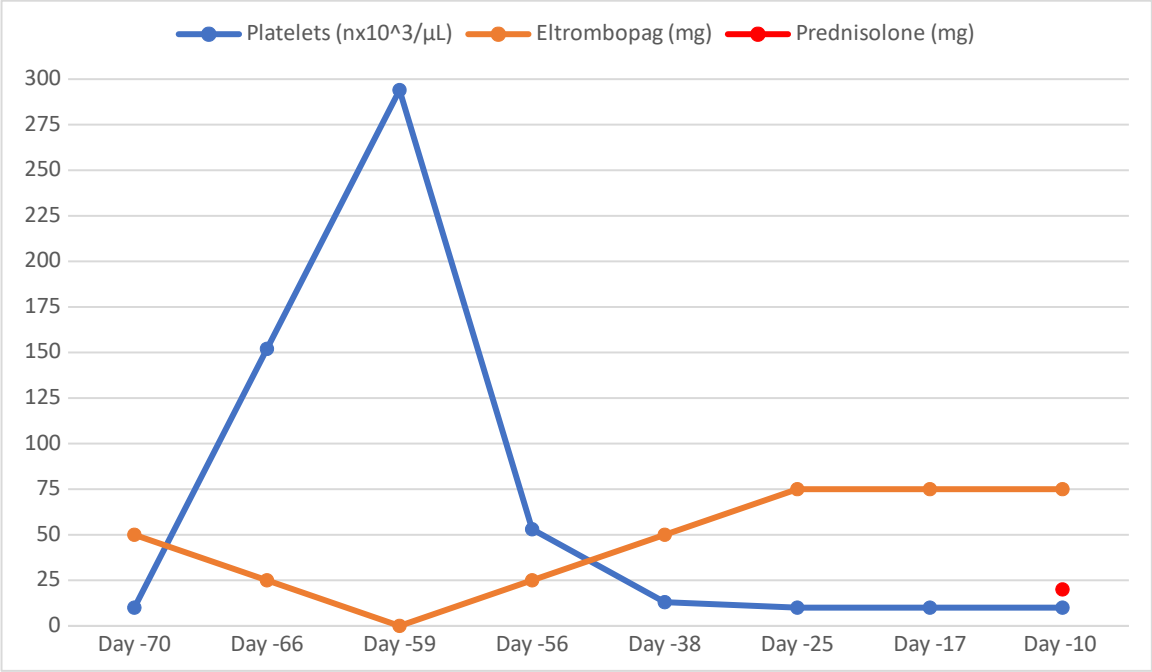
Graphic 1. Platelet count and eltrombopag dosing.



Eltrombopag (EPG) is a low molecular weight thrombopoietin receptor agonist also used as a second-line treatment for ITP, which increases the platelet count.[4] The association of this drug with thrombotic events is known. However, there are few cases of venous sinus thrombosis (VST) described in the literature.[3,5,6]

CLINICAL CASE

A 26-year-old female with a 3-day history of severe frontal headache, with phono and photophobia, nausea, vomiting, and confusion, presented in October 2019 in the emergency room.

A diagnosis of ITP was made at the age of 14 in the context of extreme metrorrhagia. She has since been splenectomized, treated with multiple courses of immunoglobulins, steroids, and rituximab, with no sustained response, presenting recurrent platelet count <5k/µL with *petechia*.

After a discussion at hematology group reunion, she was started on EPG 50mg daily at the beginning of August 2019 and oral estroprogestative to control metrorrhagia.

Two months before the presentation she showed 294k/µL platelets, suspending EPG. Two weeks after, she presented again with <10k/µL platelets and had incremented a dose of 25mg twice daily with no response. About a month before the event, she presented again <10k/µL platelets and full-body petechia. A dose increase in EPG to 75mg daily was prescribed, again with no effect, which motivated the addition of 20mg of prednisolone 2 weeks after (Graphic 1).

In the emergency department, neurological examination presented with mild paraphasias, anomalous pauses, and difficulty in reading. Routine laboratory testing was remarkable only for mild thrombocytopenia (platelet count 281k/µL) leukocytosis (13k/µL) and elevated C-reactive Protein (9mg/dL). She performed a study with brain computerized tomography (CT) and magnetic resonance that demonstrated extensive VST with left temporal hemorrhage (Figure 1).

During hospitalization, a thrombophilia work-up which included factor V Leiden, prothrombin gene mutation, and antiphospholipid antibody syndrome (lupus anticoagulant, anti-β2-glycoprotein I antibodies, and anticardiolipin antibodies) was negative.

EPG was suspended and enoxaparin 1mg/kg twice daily was started at admission. Increasing thrombocytosis was observed (maximum 1,000,000 platelets – Graphic 2) for nine days, with a subsequent decrease to normal levels. She maintained neurological deficits stability but without improvement over time. Sequenced cerebral CT showed hemorrhage reabsorption without new hemorrhagic events. She has been discharged on dabigatran 150mg twice daily.

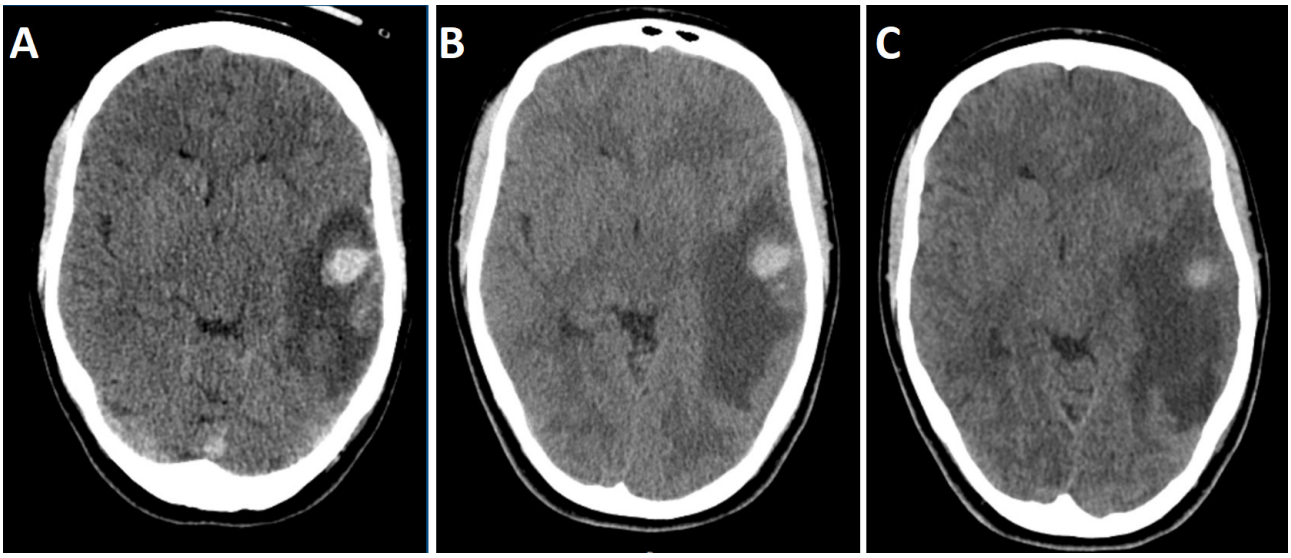
DISCUSSION

A relationship between thrombocytosis and thrombosis has not been demonstrated in patients with ITP. On the contrary, there seems to be a paradoxical relationship with thrombocytopenia, with 5% of patients with ITP experiencing thrombotic events throughout their lifetime.[2]

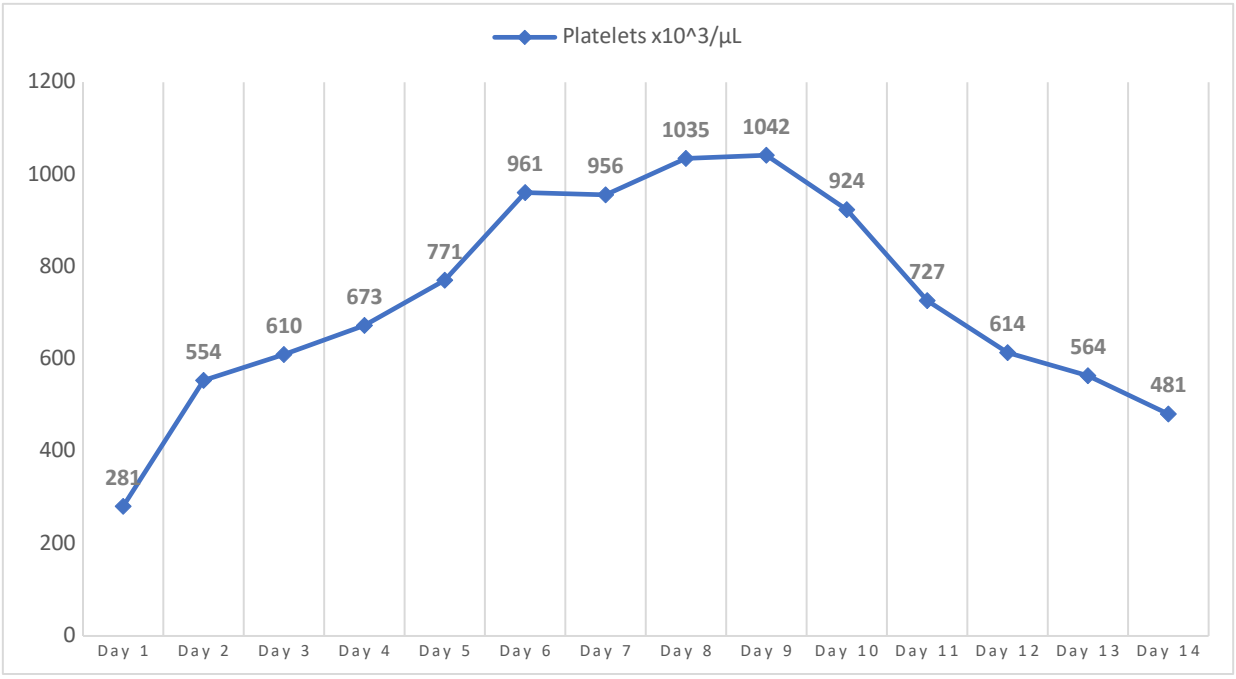
Data relating specifically to EPG are contradictory- In a study with patients treated with EPG, half of the ones who developed thrombosis were thrombocytopenic at the time of diagnosis[7] In another, there was an association between high platelet counts (>200k/µl) and the risk of thrombosis.[8]

Having a thrombotic event following multiple dose increases was described before, and it makes EPG the more likely culprit for this event.[5] Although we can't ignore the fact that our patient had two prior

Figure 1. Cerebral computerized tomography on day 1 (A), 6 (B), and 13 (C).



Graphic 2. Platelet count evolution.



risk factors for thrombosis (female and using oral estroprogestative) and also was being recently treated with steroids. The fact that the patient was under low molecular weight heparin during thrombophilia workup can be also a confounder since it can lead to false negatives.

Since the increased probability of thrombosis is demonstrated with EPG, this population should be advised to avoid prothrombotic risk factors such as smoking, obesity, oral estroprogestative, and immobilization. It is also concerning that headache and nausea, which are among the most common side effects of EPG, can be symptoms of a worse underlying problem and have to be taken seriously in EPG-treated patients.[9]

The treatment of VST is based on the use of anticoagulants, however, the use of new oral anticoagulants is controversial due to the lack of randomized studies. We chose dabigatran because of the method of administration appropriate to the patient's lifestyle, as well as the existence of a readily available antidote.

After discharge, our patient was followed by a neurology expert who suspended dabigatran after six months, with no new thrombotic events to date. She also presented with no neurological deficits at six months. A weekly appointment with a specialist hematologist was arranged. She was treated with steroids alone, then in association with rituximab and cyclosporin, both with a short response, then azathioprine monotherapy with relapse after a year. She is now enrolled in an ongoing efgartigimod clinical trial.

DISCLOSURES

Consent was obtained by the patient. The authors have no conflicts of interest to declare.

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