



IDIOPATHIC THROMBOCYTOPENIC PURPURA AND ORAL SURGERY: case report

Púrpura trombocitopênica idiopática e cirurgia bucal: relato de caso

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Abstract

OBJECTIVES: To review the function of platelets in the blood clotting mechanism. To address, conceptualize and classify thrombocytopenic purpura, especially idiopathic thrombocytopenic purpura (ITP), emphasizing the immunological aspects involved in the etiology of the disease. To address the clinical manifestations of the disease and the appropriate therapy. To present the case study of a patient with ITP who requires oral surgical intervention. **DISCUSSION:** Leukopenia in ITP can be subclinical. The first manifestation of the disease can be severe hemorrhaging due to small lacerations or minor medical and dental surgical procedures. The cause of the platelet reduction is idiopathic; an autoimmune reaction in which the antibodies destroy the platelets appears to participate in the process. A variety of situations can occur, leading to mild to severe thrombocytopenia. One frequent aspect is the instability of the platelet count, which oscillates inconsistently and may be related to infections and other factors that have not been clearly determined, including stress. In the case presented here, the leukopenia in the patient was mild in presentation. However, it was decided that the patient should be referred to a hematologist for preparation and clearance. Oral surgery that compromises the bone, such as exodontia, can present significant difficulties in localizing and clamping intraosseous vessels, which does not only occur in small soft tissue surgeries. **CONCLUSIONS:** Platelet destruction in ITP occurs from a complex process that is comprised of multiple components of the immune system. The platelets are prematurely destroyed by antibodies that are aimed at the platelet glycoprotein, which can result in serious, even fatal consequences. It is important to emphasize the significance of the medical history and the appropriate physical examination during the diagnostic process, as well as collaboration with the patient's medical clinic. The medical history should compile data such as the beginning of signs and symptoms, time of development, previous history and types of bleeding, drug intake, and the presence of other signs and symptoms, such as fever, adenopathy and anemia not only from the patient, but also from the family. The most important sign during the physical exam is the presence or report of petechiae occurrence.

Keywords: Thrombocytopenia. Idiopathic thrombocytopenic purpura. Autoimmune conditions. Hemorrhagic disorders. Oral surgery.

Resumo

OBJETIVOS: Revisar a função das plaquetas no mecanismo de coagulação sanguínea. Conceituar e classificar a púrpura trombocitopênica, especialmente a púrpura idiopática, enfatizando os aspectos imunológicos envolvidos na etiologia da doença. Enfocar as manifestações clínicas da doença e a terapia apropriada. Apresentar um caso de manifestação clínica da doença e a terapia apropriada. Apresentar o caso de uma paciente com púrpura que necessitava de intervenção cirúrgica bucal. **DISCUSSÃO:** A leucopenia na púrpura trombocitopênica idiopática pode ser subclínica. A primeira manifestação da doença pode ser uma hemorragia severa por causa de pequenas lacerações ou pequenos procedimentos médicos e odontológicos. A causa da redução das plaquetas é idiopática; uma reação autoimune na qual os anticorpos destroem as plaquetas parece participar do processo. Uma variedade de situações pode ocorrer, levando à trombocitopenia discreta a severa. Um aspecto frequente é a instabilidade da contagem plaquetária, que oscila inconsistentemente e pode relacionar-se com infecções e outros fatores ainda não claramente determinados, incluindo estresse. No presente caso, o paciente apresentava discreta leucopenia. Entretanto, decidiu-se que o paciente deveria ser avaliado por um hematologista, para preparação e liberação para cirurgia, pois a cirurgia bucal que compromete osso, como a exodontia, pode apresentar dificuldades significativas na localização e pinçamento de vasos intraósseos, o que não acontece em pequenas cirurgias de tecidos moles. **CONCLUSÕES:** A destruição plaquetária na púrpura trombocitopênica ocorre por meio de um complexo processo, com múltiplos componentes do sistema imune. As plaquetas são destruídas prematuramente por anticorpos dirigidos contra as glicoproteínas plaquetárias, o que pode resultar em sérias – e mesmo fatais – consequências. É importante enfatizar o significado da história médica e o exame físico adequado no processo diagnóstico, bem como a participação do clínico geral do paciente. A história médica deve compilar dados tais como início dos sinais e sintomas, tempo de evolução, prévias histórias e tipos de sangramento, uso de drogas e presença de outras manifestações, como febre, adenopatias e anemias, não somente no paciente, mas também na família. O mais importante sinal durante o exame físico é a presença ou relato da ocorrência de petequias.

Palavras-chave: Trombocitopenia. Púrpura idiopática. Condições autoimunes. Desordens hemorrágicas. Cirurgia bucal.

INTRODUCTION

Platelets have a fundamental function in the blood clotting system and participate in the initial phase of the hemostatic process through adhering to the collagen and aggregating to form the clot (“cork”) in the exact location of the vascular lesion. Therefore, any factors that perturb platelet physiology can have immediate results on the general process of coagulation. Much later, during coagulation itself, platelets continue to exert an important function for the release of platelet factor 3, which facilitates the interaction of diverse factors of coagulation in the complex cascade mechanism (1).

Platelet purpuras can be caused by a reduction in platelet numbers, which is called thrombocytopenic purpura. Nonthrombocytopenic

purpuras are when platelet numbers are normal or below normal and have altered functions, which manifest as hemorrhagic disorders.

In regard to this case study, only thrombocytopenic purpura will be considered. The classification of thrombocytopenic will treat the cause of purpura as an *increase in platelet destruction* by an autoimmune mechanism.

Idiopathic thrombocytopenic purpura (or autoimmune) (ITP) is an acquired disease that is characterized by mild to severe thrombocytopenia, although the bone marrow is in relatively normal condition, and by muco-cutaneous bleeding with the absence of other abnormalities. The platelet number can be in a normal or below normal range; however, the function of the platelets can be altered and manifest as a hemorrhagic disorder (2).

Blood clotting mechanism

For the best understanding of the role of platelets and its glycoprotein complex in coagulation, some considerations are necessary in respect to the blood clotting mechanism. Coagulation is a number of complex interactions in which blood loses fluidity and is converted into a semi-solid mass, forming the clot, which is irreversible. Clot formation transpires from the interaction of injured tissue, the platelets and fibrin (3).

The biochemical formation of the clot involves complex *protein-protein* interactions. Basically, this is the conversion of soluble proteins from the plasma (the fibrinogen) into fibrin by the action of an enzyme called *thrombin*. This is formed by a series of sequential activation stages: the substrate for each enzyme is a pro-enzyme, which is activated in the next stage of the reaction. This reaction sequence is called the *coagulation cascade*, which terminates with the formation of thrombin (4).

The first thrombin links that are formed at the injury stimulate platelet responses. After the injury, the platelets accumulate together in a mass at the vessel wall as a result of platelet adherence to collagen in the exposed endothelial tissue (*adhesion*) and afterwards between themselves (*cohesion or aggregation*). They form the so-called primary plugs. With the increase of thrombin concentration at the injury area, the loosely adhered platelets (in the primary plugs) consolidate into a stable plug. Then, the plug forms, along with fibrin on the surface of the aggregated platelets, and afterwards, it is like a network that spreads out, which reinforces the plugs that promote hemostatic sealing.

The platelets contain glycoproteins that are rich in carbohydrates, and they are situated in an amorphous outer-coating (glycocalyx) and an underlying membrane unit that is constituted by a *phospholipid bilayer*. The various glycoproteins are GP I, II, and III; GPIb; GPv; and GPIIb, and IIIa (4).

The connection areas on the outer surface of the membrane, which are essential for the normal function of the platelets, were identified in the GPIb and a GPIIb-IIIa complex that is formed during platelet activation. The platelet glycoprotein IIb/IIIa complex has an essential role in the thrombus formation that is mediated by the platelets (5).

However, in the case of autoimmune thrombocytopenia (ITP), where the platelets have been opsonized by platelet antibodies that are aimed at diverse platelet glycoproteins including GPIIb/IIIa and GPIb/ix and are prematurely destroyed by the mononuclear phagocyte system (old reticulo-endothelial system) of the pancreas, liver or bone marrow, there is not a sufficient number of circulating platelets at the vascular injury (6). In short, ITP is an acquired chronic autoimmune disorder in which the platelets suffer attack (opsonization) by *platelet antibodies* that are aimed at these glycoproteins on the surface of platelets.

This occurs in small children and is generally accompanied by a viral infection because the viral antigens are connected to the platelet surface. It is important to note that besides phagocytosis, the destruction mechanism also includes activation of the complement abnormalities of T cells, the discussion of which extends beyond the limits of this work (7).

Although historically, chronic idiopathic thrombocytopenic purpura is only associated with increased ratios of antibodies versus platelets, it has become evident that deficient thrombopoiesis is also important in the pathogenesis of this condition (8).

Because of the limitations of this work, deficient thrombopoiesis will not be addressed in depth. The etiology of ITP in adults is unknown. The diagnosis of ITP is from exclusion; its clinical development is variable and unpredictable (9). Although it is generally considered a disorder of young adults, with increased prevalence in women, it also occurs in the elderly (10).

The study of thrombocytopenic purpura has great importance because hemorrhagic disorders are the most frequently seen in both medical and dental clinical practice. The decrease in the number of platelets is parallel to the decrease of platelet functions, which leads to the hemorrhagic state (11).

Clinical manifestations of ITP

The clinical presentation of ITP can be *asymptomatic*, it can present as *small petechiae* and mild skin and mucus bleeding or it can present as *intense and serious blood loss* to the point of threatening life. ITP can occur at any age, but it is more common in children and adolescents and

shows an increased prevalence in females. As stated above, its cause is unknown, although there is evidence of genetic predisposition (12).

The patient's clinical history is fundamental for the diagnosis of ITP, and an inquiry for data related to the beginning of the signs and symptoms, development, duration period, previous episodes of bleeding (in the patient or family), medication intake, drug addiction and the presence of other symptoms and signs, like fever, anemia and adenopathy, should be performed (9).

The type of bleeding is important data that should be considered. Types of bleeding include cutaneous (petechiae, bruises or hematomas), digestive (melena), urine (hematuria), genital (metrorrhagia) or the gravest-bleeding of the central nervous system, with presentation of convulsions, which could develop into loss of consciousness and coma.

An important symptom is the presence of petechiae, which can indicate capillary bleeding; this is a main injury in the initial or primary phase of hemostasis, and it is common in thrombocytopenia. However, petechiae are not only constituted in the manifestation of cutaneous bleeding. They can appear in mucous bruising, hematomas or bleeding (nose, gums, gastrointestinal and genitourinary) (9).

Beyond hemorrhagic signs, other signs and symptoms can be present: fever, lymph nodes, hepatosplenomegaly, joint pain, erythematous skin lesions and others that can identify some base pathology, as in the cases of secondary thrombocytopenic purpura (11).

Laboratory exams

The complete blood count (CBC) is useful in the diagnosis of ITP, because it not only provides an orientation about existing anemia and its level, but also provides further information about the leukocyte number and its changes. However, the reduced number of platelets is what supports the diagnosis of thrombocytopenia. A morphological exam of the platelets can indicate if there are anomalies (micro or macro-platelet).

When platelet levels are between 50,000 and 100,000/mm³, mild clinical manifestations can occur because the platelets still maintain the capacity for hemostatic equilibrium. Generally,

when the platelet number is below 50,000/mm³, it suggests purpuric manifestations. Below 30,000/mm³, the symptoms and signs are more intense; when between 10,000 and 5,000/mm³, the hemorrhagic phenomena can be grave (11).

Platelet function is evaluated by bleeding time (BT), which can be prolonged in accentuated thrombocytopenia (> 5 min), as well as clot retraction, which can be deficient or absent with only a slight absorption of prothrombin one hour after coagulation. The identification of an autoimmune process is investigated by the presence of antiplatelet antibodies by using the platelet-associated *immunoglobulin-G (PA-IgG) technique (direct or indirect methods)*. *Shortened platelet survival indicates the presence of platelet destruction due to immune and splenic sequestration.*

In some cases, examination of the bone marrow examination is very important; this should be conducted when the cause of thrombocytopenia is unclear. Study of the bone marrow should be directed to the megakaryocytes, which are the cells from which platelets are produced. If they are reduced, this can confirm thrombocytopenia by reduction in the production of platelets (12).

Hypoproduction can occur when the marrow presents an intrinsic anomaly, either primary (genetic or idiopathic disorders) or secondary (marrow injury by drugs, infections, chemical agents) or marrow infiltration (neoplasms).

Platelet destruction, in an acute process, causes the number of megakaryocytes to increase by three or four times in the marrow; the number can be up to eight times the normal value in chronic processes. There is platelet production, but with rapid destruction by an immunological mechanism or isolated absorption (12).

A phenomenon particularly inherent to ITP is the triggering of the immunological reaction by unknown factors and situations; therefore, ITP is totally unpredictable, and the factors are as varied as an increase in stress, physical exhaustion and viral diseases.

Treatment of ITP is the responsibility of a hematologist. Two courses of treatment are necessary when dealing with an ITP patient. The first is the treatment of the disorder itself with diverse techniques, including: hospitalization, platelet transfusion, corticosteroids and diverse other drugs. Additionally, a splenectomy is necessary in thrombocytopenic cases that do not

respond to clinical therapy in the first six months of treatment (general platelet count is below $10,000/\text{mm}^3$) (12).

Another focus is the treatment of the asymptomatic or episodic ITP patient, which necessitates undergoing elective and open oral intervention. These patients generally do not present consistent thrombocytopenia at an excessively low level; in the acute phase of ITP they are below $100,000/\text{mm}^3$, and the majority reach a lower limit of $50,000/\text{mm}^3$ (12).

It is evident that the early diagnosis of the disorder, or its identification in a patient's medical history, and preparation of the patient for open dental intervention is of extraordinary importance in order to avoid trans- and post-operative problems, which can be of extreme gravity. Even in asymptomatic ITP, with the mildest of manifestations such as small petechiae or bruises, a simple extraction can lead to a hemorrhage that is difficult to control.

CASE REPORT

A 29-year-old leukoderma female patient was attended to at Urgent Care Unit of the Hospital Cajurú, Curitiba, and presented with an odontogenic infection (abscess) compromising an upper molar. In her medical history, she reported that she was a carrier of a hemorrhagic disease. Utilizing this information, she was medicated with antibiotics and analgesics, and she was sent to the Stomatology Clinic of the Dental School of the PUCPR.

At the Stomatology Clinic, her clinical history was expanded, and the following data were obtained: idiopathic thrombocytopenic purpura carrier, autoimmune; was under the care of a hematologist; had undergone a neurological surgery some years beforehand, at which time the purpura was diagnosed and treated with a platelet transfusion (in emergency); she stated that she has a son, and since his birth, she has not needed platelet transfusion because the condition had only been regulated by her hematologist pre-partum. The patient signed the adequate informed consent for treatment.

A CBC was conducted; the platelet count was $80,000/\text{mm}^3$. The other CBC data were within the normal parameters. Due to this presentation, the patient was sent to her hematologist, where

clinical preparation for oral surgery (tooth extraction and removal of focus) were requested. After 30 d, the patient returned with medical clearance for the surgical procedure. A new CBC showed a platelet count of $140,000/\text{mm}^3$. The recommended and adopted treatment by the hematologist was conservative.

Owing to a satisfactory condition, the surgery was conducted under local anesthesia (extraction of the upper molar and alveolar curettage; suturing with 4-0 silk thread). Trans-operative bleeding was normal with a bleeding time (BT) of six minutes, which was within the normal limits. In addition, post-operation hemorrhage did not occur, and the alveolar repair process was normal.

DISCUSSION

Idiopathic thrombocytopenia purpura constitutes a disturbance in which platelet reduction exists without an apparent cause, which can result in abnormal hemorrhaging. The cause of platelet reduction is unknown (idiopathic), but an abnormal immune reaction (autoimmune reaction) of platelet destruction by antibodies appears to participate in the process. Although the bone marrow increases platelet production in order to compensate for the destruction, the supply is inferior to the demand. In children, this disturbance habitually appears after a viral infection and disappears without any type of treatment after some weeks or months.

In adults, it occurs in a variety of situations, from mild to severe thrombocytopenia, with mild clinical manifestations. A frequent aspect of the disease is platelet count instability, which inconsistently oscillates, and may be related to infections and other factors that are not well determined, including stress. Leukopenia in ITP can present in a subclinical form, and its first manifestation can be a severe hemorrhage due to lacerations or minor medical and dental surgical procedures.

In the case presented herein, the patient knew her condition and was under the care of a medical specialist, a fact that greatly facilitated the management of the disease and led to the oral surgery recommendation.

Although thrombocytopenia was verified in the first CBC ($80,000/\text{mm}^3$), it was considered mild (11) and-theoretically-allowed for only a small

oral surgical intervention (through maintenance of the hemostatic balance capacity). Therefore, it was decided that the patient should be referred to a hematologist for appropriate preparation and clearance. It is important to remember that oral surgery with compromised osseous can present significant difficulties in localizing and clamping intraosseous vessels, which does not exclusively occur only in minor surgeries of soft tissue.

Various options for the treatment of ITP exist, which are all the responsibility of a hematologist, that depend on the severity of the condition and also on any surgical procedures that have been indicated for these patients. Some of these options include (12):

- increase platelet supply (platelet transfusion);
- increase platelet production (bone marrow transplant; corticosteroids);
- interference in T- or B- cell participation in antibody synthesis (Rituximab; intra venous immunoglobulin);
- nonspecific immunosuppression of T-cells (corticosteroids; cyclosporine);
- radical treatments, such as splenectomy or corticosteroids at high doses;
- the conventional course in the case of patients that present great oscillations in platelet count, searching to eliminate predisposing factors and waiting for the appropriate moment for necessary invasive intervention.

In the case study, the hematologist opted for the conventional course because surgical intervention (exodontia) was not urgent, which allowed for the normalization of the platelet count. Thrombocytopenia of a mild nature presented during the initial consultation and developed satisfactorily in 30 d (80,000/mm³ to 140,000/mm³); this response was obtained principally by controlling stress. According to the related medical history, this course has already been demonstrated to be effective in the past (i.e., during the birth of the patient's son).

CONCLUSION

Platelet destruction in ITP occurs due to a complex process that involves multiple

components of the immunological system. In autoimmune thrombocytopenia, the platelets are prematurely destroyed by platelet antibodies that are aimed at diverse platelet glycoproteins, including BPIIb/IIIa and GPIb/ix. As such, there is not a sufficient number of circulating platelets at the vascular injury. ITP can become a problem with serious consequences, including fatal, if oral surgical intervention is not previously diagnosed because the disease can be asymptomatic and the patient is unaware of the condition.

The importance of collecting the medical history and appropriate physical exam during the diagnostic process, as well as fundamental and close collaboration with the patients' clinicians, must be emphasized. They should compose the medical history and inquiry for data such as beginning of signs and symptoms, development time, previous history and types of bleeding, drug intake, and the presence of other signs and symptoms, like fever adenopathy and anemia not only from the patients, but also from their families. The most important sign in the physical exam is the presence or a reported occurrence of petechiae.

CONFLICT OF INTEREST STATEMENT

The authors formally declare that there is no conflict of interest in the present manuscript.

INFORMED CONSENT STATEMENT

The patient signed an informed consent, kept in the records in the archives of the Faculty of Dentistry, PUCPR, Brasil.

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