

# Dengue and Immune Thrombocytopenic Purpura

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## Abstract

The year 2003 in the State of Rio de Janeiro was marked by a dengue epidemic caused predominantly by DENV-3. This occurrence had some atypical manifestations of the disease, among which included hepatitis, encephalitis and immune thrombocytopenic purpura (ITP). It is known that ITP, following viral infection generally, occurs in children and has an acute course. On the other hand, ITP in adults has a chronic course and is not often associated with viral infections. In this article, a case of chronic ITP in an adult woman that occurred after infection by the dengue virus (DENV-3) is described.

**Keywords:** Dengue, DENV-3, immune thrombocytopenic purpura (ITP), Brazil.

## Introduction

It is known that immune thrombocytopenic purpura (ITP) can be both primary and secondary. The secondary form of this disease may occur in association with systemic lupus erythematosus, antiphospholipid antibody syndrome, immunodeficient states, lymphoproliferative disorders, viral infections and therapy using drugs such as quinidine, sulfa and heparin. ITP can also be classified as either acute or chronic. The acute forms of ITP are more common among children, generally following viral infection, and tend to have a self-limited nature in up to 80% of the cases. On the other hand, ITP in adults almost invariably has a chronic course and requires treatment to obtain remission of the signs and

symptoms. ITP in adults is rarely associated with viral infections.

In this article we report on a case of chronic ITP in an adult that appeared following a condition of viral infection (classic dengue) in a way that was similar to what happens in the majority of acute ITP cases among children. The physiopathogenesis, diagnosis and treatment of this haematological disorder will be discussed.

## Case Report

In 2003, during a dengue epidemic caused predominantly by DENV-3, a 47-year-old woman presented a clinical condition of fever,

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headache, arthralgia, myalgia, anorexia, retro-orbital pain, nausea, prostration and bitter taste in the mouth. This woman (TCFT) was a domestic employee and a native of Campos dos Goytacazes, State of Rio de Janeiro, Brazil, with no recent history of travelling. On the eighth day of the illness, when she was already presenting a clinical improvement, the patient sought assistance at the Dengue Reference Center to find out the cause of her illness. From the epidemiological pattern and the symptomatology presented, dengue was the first diagnostic hypothesis. The woman said that she had used dipyrone and paracetamol, but said that she had not made any regular use of any other drug before the onset of symptoms.

The physical examination performed at this first consultation presented evidence of a positive 'tourniquet test' without other abnormalities. Thus, complementary laboratory tests were requested and the patient was released and given advice. It was only on the ninth day of the illness that she complained of bleeding gums and haematochezia, when she was hospitalized. Upon physical examination, she was found to be lucid and aware of her surroundings, eupneic, pale colouration (+/4+), unjaundiced, hydrated, acyanotic and non-febrile. In her cardiovascular system, she had a regular heartbeat, normal heart sounds, systemic arterial pressure of 110 x 80 mm Hg, and a heart rate of 80 beats per minute. In her respiratory system, she had a vesicular murmur that was audible bilaterally, without extraneous noise. Her abdomen was flaccid and painless upon palpation, without enlarged organs. Her lower limbs did not present any abnormalities. The laboratory test results were: leukocytes 3510 (rods 0, segmented leukocytes 1404, lymphocytes 1509, monocytes 280, eosinophils 210 and basophils 0), haemoglobin (Hb) 9.1, haematocrit (Ht) 28.7%, slight microcytosis, platelets 24 100, VHS in the first

hour 40 mm, AST (TGO) 35, ALT (TGP) 21, glycoside 80 mg/dl, urea 17.4 mg/dl, creatinine 0.58 mg/dl, calcium 7.9 mg/dl, K<sup>+</sup> 4.4 mEq/l, Na<sup>+</sup> 143 mEq/l, TAP 100% – 12s, PTTa 33s (INR = 1).

Thus, a case of classic dengue with haemorrhagic manifestations was diagnosed, as per the World Health Organization (WHO) criteria<sup>[1]</sup>, from the DENV-3-specific IgM serology using the MAC-ELISA reagent, with a blood sample collected on the eighth day after the onset of the symptoms.

The patient showed good recovery and was discharged from hospital for outpatient follow-up.

On the 25<sup>th</sup> day after the onset of the symptoms, the patient returned to the outpatient service of the Dengue Reference Center with a complaint of dizziness, headache, myalgia, severe asthenia, dyspnea and hypermenorrhoea. She was hospitalized again for a new diagnostic investigation. At the time of second hospitalization, she presented anaemia (Hb 6.5, Ht 20.3%) and low platelet count (11 500/ $\mu$ l). After clinical stabilization and improvement in the laboratory parameters, the patient was again discharged for subsequent outpatient follow-up, with a diagnosis of primary post-dengue low platelet count.

On the 35<sup>th</sup> day after the onset of symptoms, the patient presented slight gum bleeding, macroscopic haematuria and ecchymosis in her left arm and thigh, and also petechia on her legs. The laboratory tests showed: leukocytes 7420, Hb 12.2, Ht 37.7, platelets 22 600, TAP 100% – 12 s, PTTa 33s (INR = 1). Blood tests for systemic lupus erythematosus, HIV, hepatitis C and antiphospholipid antibody syndrome were negative. A myelogram showed hyperplasia of the megakaryocytic sector.



On the basis of this patient's clinical history, in which she said that she had not had any skin or mucosal haemorrhagic manifestation or abnormalities in laboratory tests prior to this clinical condition, the hypothesis of primary post-dengue ITP was thought of by excluding the other possibilities. Thus, specific medication for this was instituted (prednisone 1 mg/kg/day). The steroid dose was gradually reduced, with a consequent fall in the platelet count, and it was necessary to maintain a dose of 20 mg on alternate days so that the response would be sustained. Since then, there have not been any spontaneous haemorrhagic events. After one year and three months, laboratory tests showed: Ht 34.2%, Hb 11.2, platelets 109 000 and leukocytes 8000.

## Discussion

Immune thrombocytopenic purpura is an auto-immune disorder characterized by low platelet count and skin-mucosal bleeding. In a study carried out between 1973 and 1995, the incidence of ITP among adults was estimated as 32 cases per million persons per year<sup>[2]</sup>. It generally affects adults in an idiopathic and chronic manner, and it is found twice as frequently among women as among men. In contrast, ITP is frequently acute among children, with a condition of petechia or purpura appearing a few days or weeks after an infection that, in most cases, is viral<sup>[3]</sup>.

Thrombocytopenia associated with viral infection seems to result both from a reduction in the production of platelets from megakaryocytes and from a decrease in the half-life of the platelets. The latter is the principal mechanism<sup>[4]</sup>. Platelets that are sensitized by autoantibodies are destroyed by cells of the reticuloendothelial system, particularly those of the spleen<sup>[5,6]</sup>. These autoantibodies against glycoproteins of the platelet membrane can be identified in 80% of the patients<sup>[7,8]</sup>.

A variety of viruses have already been implicated in the etiopathogenesis of ITP, especially in children: HIV-1<sup>[9,10]</sup>, hepatitis C virus<sup>[3]</sup>, varicella-zoster virus<sup>[11,12]</sup>, rubella<sup>[13,14]</sup>, influenza<sup>[15]</sup> and Epstein-Barr virus<sup>[16]</sup>.

In 1993, Leong and Srinivas<sup>[17]</sup> reported on the case of a girl aged 15 years who presented prolonged thrombocytopenia following infection by the dengue virus (haemorrhagic form). The mechanism was presumed to be immunological, and the patient responded well to treatment using steroids.

The diagnosis of ITP is achieved by ruling out other possibilities. Other causes of thrombocytopenia should be investigated, such as: systemic lupus erythematosus, HIV/AIDS, pregnancy, use of medications (heparin, sulfa and quinidine) and recent blood transfusion, among others<sup>[3,18]</sup>.

The duration of the bleeding helps in distinguishing between the acute and chronic forms. Detailed history-taking is important in order to obtain information on drug use and family history. The presence of splenomegaly may be found in up to 10% of cases. If this is found, a diagnosis of some other disease should be considered<sup>[19]</sup>. In prick tests for evaluating peripheral blood, immature platelets are frequently observed (megathrombocytes). Such tests are also useful for ruling out pseudo-thrombocytopenia and other haematological causes<sup>[3]</sup>.

According to the guidelines of the American Society of Hematology, bone marrow aspirate is unnecessary among adults aged less than 60 years but is appropriate before splenectomy<sup>[18,20]</sup>. The presence of fever, joint pains, neutropenia or unexplained macrocytosis makes bone marrow examination essential<sup>[3]</sup>.

The main objective in treating ITP is to achieve stabilization of the platelet count at a level that would prevent a major risk of



bleeding. Many authors have reported that it is important to avoid unnecessary treatment for asymptomatic patients with moderate thrombocytopenia. Moreover, the efficacy of the therapy is uncertain among asymptomatic patients with severe thrombocytopenia. Such patients have reported that the morbidity related to the side-effects exceeds the problems caused by the disease itself<sup>[20]</sup>.

Immune thrombocytopenic purpura in adults generally requires treatment using oral prednisone at the time when it is presented (at a dose of 1 to 1.5 mg/kg/day)<sup>[20]</sup>. Most adults with ITP generally start to respond to prednisone after two weeks of treatment<sup>[21,22]</sup>. Patients who continue to show symptoms and who have severe thrombocytopenia (platelet counts of less than 10 000/ $\mu$ l) after this time can then be assessed for the possibility of splenectomy. Anti-D immunoglobulin, despite being less toxic and equally effective for Rh-positive patients, is considerably more expensive<sup>[20,23]</sup>.

Intravenous immune globulin (1 g/kg/day for 2 to 3 consecutive days) is used for treating internal bleeding when the platelet count is less than 5000/ $\mu$ l despite corticoid therapy for many days, or when there is progressive or extensive purpura<sup>[24]</sup>.

The decision to perform splenectomy depends on the severity of the disease, the tolerance towards corticoids and the patient's willingness. Although it is recommended when there is a need for more than 10 to 20 mg of prednisone per day for a three- to six-month period in order to maintain the platelet count above 30 000/ $\mu$ l, present-day data have demonstrated that an expectant approach is more appropriate<sup>[3]</sup>.

In the present case of dengue reported, there was no platelet count record from before the disease, or for the first seven days after the onset of symptoms. However, considering this to be a primary case of infection by the

dengue virus, it is possible that the attack on the platelets initially took place through dysfunction of the megakaryocytes and direct damage to the platelets by the virus itself<sup>[25]</sup>. The perpetuation of the low platelet count probably occurred through immunological mechanisms, thus characterizing a condition of post-dengue ITP. The presence of signs of skin-mucosal bleeding only on the ninth day of the disease supports this diagnosis, given that immune thrombocytopenia characteristically first appears between the seventh and tenth day of illness<sup>[26]</sup>, which is different from the thrombocytopenia inherent to an infectious condition, which occurs earlier.

## Conclusion

ITP in adults is generally a chronic and idiopathic disease. However, as could be seen in the present case, it may also occur in a chronic form, but following viral infection, in a mixture between the adult and child forms of ITP. The factors that determine whether post-viral thrombocytopenia will follow an acute or chronic course remain unknown. It is thought that, in some immunologically predisposed individuals, the persistence of virus-induced antibodies against the platelets is the agent responsible for a chronic course of thrombocytopenia rather than an acute course<sup>[2]</sup>.

The State of Rio de Janeiro, just like much of Brazil, suffers from economic and structural difficulties related to the health care system in relation to the spheres of prevention and cure. There are often difficulties in achieving adequate practice of medicine because of the lack of human and/or material resources for attending to a large part of the population. Thus, the reporting of this case becomes important since it enables us to share medical-scientific knowledge with professionals in other communities, particularly those that resemble ours with regard to epidemiological and socioeconomic conditions, such as in South-East Asia.



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