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# Clinical features and management of pediatric patients with primary immune thrombocytopenia in a secondary care hospital in Northwest Mexico

## Abstract

**Introduction:** Primary Immune Thrombocytopenia (PIT) is considered the most common immune hematologic disorder in children and represents a risk of morbid mortality. Despite it being a common diagnosis, its epidemiological characteristics have not been studied in our hospital.

**Objective:** To determine the clinical and laboratorial characteristics of pediatric patients with PIT treated by the hematology service over a period of four years.

**Material and methods**: This study was a retrospective analysis of pediatric patients with PIT who attended at the hematology service from 2014 to 2018 in the Gyneco-Obstetrics and Pediatric Hospital No. 31 in Mexicali, Baja California, Mexico. Medical history, clinical manifestations, laboratory results, treatment and therapeutic response, as well as recurrence and PIT classification were analyzed from their clinical files. Descriptive statistics was used, with measures of central tendency, percentages and frequencies with the SPSS v25 program.

**Results:** A total of 57 patients were studied. The mean of age was 6.8±4.2 years, newly diagnosed PIT was present in 93.0% (n=53). The majority of patients were managed with observation alone (40.4%, n=23). The most frequent pharmacological managements used were intravenous immunoglobulin (29.8%) and steroids (19.3%). Recurrence was present in 12% of cases; 7% developed chronic PIT.

**Conclusion:** The pattern of clinical and laboratory characteristics observed in this study are mostly similar to national and international literature. A remarkable finding was the few cases of chronic PIT.

**Keywords:** thrombocytopenia, pediatrics, hemorrhage, epidemiology

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## Introduction

Primary immune thrombocytopenia (PIT) is a hematological disorder characterized by isolated thrombocytopenia in absence of other causes that may be associated with thrombocytopenia.[1] The incidence of PIT in the pediatric population in the United States is 1 case per 100,000 children.[2] There is no Mexican epidemiological census to compare it to.[3] PIT is an autoimmune disease in which platelets are destroyed prematurely, due to the binding of an IgG antibody in response to an unknown stimulus. Cytotoxic mechanisms and reduction of platelet production have also been thought to be involved.[2] Usually, signs of PIT begin with an acute onset of ecchymosis or petechial rash occur in previously healthy children. It affects both genders equally but there is predominance in men in patients under 10 years of age. The mean age of onset is 6 years.[4] In most cases, manifestations are preceded by an infection, commonly an upper respiratory tract infection.[5] Their appearance has also been associated with the application of the MMRV vaccine.[6] The physical examination, in most cases, only shows skin involvement. However, other hemorrhagic manifestations, including epistaxis and hematuria, may also occur to a lesser extent.[7] In almost a third of cases, thrombocytopenia can be an incidental finding in routine examinations or, during the investigation of other diseases, and until then, patients have been asymptomatic.[8] To establish a diagnosis, secondary causes of immune thrombocytopenia should be ruled out, mainly autoimmune diseases (antiphospholipid syndrome) and viral infections (hepatitis C, HIV). Medical history, physical examination, complete blood count and peripheral blood smear are necessary to make the diagnosis.[9] Once the diagnosis is made, a classification is made according to the time between diagnosis and a complete response (platelets ≥100x109/L): newly diagnosed (≤ three months), persistent (three to twelve months) and chronic (greater than a year).[7] The treatment of PIT aims to achieve a platelet count associated with adequate hemostasis, not a "normal" platelet count. The American Society of Hematology (ASH) newest guideline suggests a stepped approach that evaluates the characteristics and needs of patients. The first-line treatment in children include: intravenous immunoglobulin (IVIg), steroids, anti-D immunoglobulin. To treat chronic forms, second-line therapy is recommended, which includes dexamethasone at high doses, rituximab and splenectomy.[1]

Female gender, age ≥11 years at diagnosis, absence of recent infection or vaccination, insidious presentation, diagnostic platelets ≥20 x 109/L and combined treatment with IVIg and methylprednisolone increases the risk of developing chronic PIT. On the other hand, mucocutaneous bleeding and treatment with IVIg seem to prevent the development of the disease.[2] The multicentric study conducted by Meillón et al.,[10] in Mexico in 2014, found that 66.7% of the surveyed hematologists indicated that the treatment of patients with PIT was done by using international guidelines.[10] The Mexican Clinical Practice Guideline (MCPG) for the diagnosis and treatment of PIT was last updated in 2009 and differs from current international

guidelines and supports the use of more aggressive lines of treatment (danazol, antifibrinolytic agents, transfusion therapy).[11] According to the pediatric service census, PIT is the most common hematological dianosis in the Gyneco-Obstetrics and Pediatric Hospital No. 31 (HGP No. 31, for its acronym in Spanish) of the Mexican Institute of Social Security. The objective of this study was to determine the clinical and laboratory characteristics of pediatric patients with Primary Immune Thrombocytopenia treated by the hematology service in our hospital.

## Material and methods

This study was a retrospective analysis of the clinical and laboratory characteristics of pediatric patients with primary immune thrombocytopenia treated in the hematology service of the Gyneco-Obstetrics and Pediatric Hospital No. 31 of the Mexican Institute of Social Security, in Mexicali, Baja California, Mexico, from July 2014 to August 2018. This study was conducted in accordance with the ethical principles of the Helsinki Declaration and Mexico's General Health Law regarding research. Authorization to conduct the study was granted by the Local Research Committee of our institution. We reviewed medical records of patients with PIT diagnosis who were treated at the pediatric hematology service during the study period. The inclusion criteria were: male or female patients, age 0 to 16 years, and confirmed diagnosis of PIT. Patients were not included if files had incomplete information. After applying these criteria, 7 cases were excluded.

The studied variables were: age at diagnosis, gender, date of diagnosis, initial platelet count, clinical manifestations, type of onset of the disease, history of infection or vaccination, initial treatment, response obtained to the first-line treatment, date of response, recurrences, second-line treatment, response to second-line treatment, use of danazol, blood transfusions or combination therapy of IV Ig and steroids, and finally, length of patient follow-up. Descriptive statistics were used: measures of central tendency, frequencies and percentages were applied to qualitative variables. The information collected was analyzed in the statistical program SPSS version 25.

## Results

Our search allowed us to identify 64 records of pediatric patients with diagnosis of PIT. After applying the inclusion and exclusion criteria, we analyzed 57 records in detail. 56.1% patients were boys and 43.8% were girls. The mean age of patients at diagnosis was 6.8±3.1 years. Medical history revealed 19.3% had a history of infection four weeks prior to diagnosis and 3.5% started symptoms during a six week period after an MMR vaccine application. The platelet count at diagnosis varied from 0 to 95 x 109/L, with a median of 11 x 109/L. The distribution by thrombocytopenic severity was as follows: 3 patients (5.3%) had severe (25 to <50 x 109/L), 4 (7%) had moderate (50 to <75 x 109/L) and 14 (24.6%) had mild (<100 to 75 x 109/L) thrombocytopenia. The onset of symptoms was acute in 34 patients and in 7 it was insidious. The remaining 16 patients (28%) did not have clinical manifestations and their diagnosis was incidental. Mucocutaneous manifestations (petechiae, ecchymosis, or epistaxis) were the most common, being present in 70.2% of cases; only one patient (1.8%) presented menorrhagia as a sign of PIT. Treatment administered after diagnosis consisted of observation (40.4%), IV Ig (29.8%), steroids (19.3%) and combined IVIg and steroid therapy (10.5%). Blood transfusions were prescribed in 7 patients. The first laboratory control was taken, on average, 9 days after diagnosis, with a range from 1 to 90 days, according to each case. On average, control in hospitalized patients was measured in 4 days and in outpatient care in 29 days. According to this control, 71.9% presented a complete response, 24.6% a partial response and 3.5% had no response. Seven patients (12%) presented complete loss of response in subsequent controls. For the treatment of recurrences, two patients (3.5%) remained under surveillance, two (3.5%) received steroids and one (1.8%) IV Ig. The remaining five (8.8%) patients received some type of combination therapy (1 steroids and IVIg, 1 steroids and danazol, 1 steroids and splenectomy, 2 danazol and splenectomy).

All patients with relapse had a complete response to second-line treatment. The time needed in order to obtain a complete response varied from 1 to 630 days, with a median of 36 days (5.1weeks). Table 1 shows the most important clinical and laboratory characteristics of the total population and according to the form of PIT they presented. Of the four (7%) patients with chronic PIT, two were subsequent candidates for treatment with rituximab due to frequent complete response losses. Complete follow-up, defined as twelve months after complete response, was achieved in 42.1% (n=24) of cases; 47.4% (n=27) had incomplete follow-up. The remaining 10.5% (n=6) remains under surveillance. There were no deaths associated with PIT diagnosis and none of the patients underwent emergency splenectomy or presented severe complications.

**Table 1** Characteristics of patients with PIT

| Features, n(%)* | Study population (n=57) | Newly diagnosed PIT (n=53) | Chronic PIT (n=4) |
|---|---|---|---|
| Gender, male/female | 32 (56.1)/25(43.9) | 30 (56.6)/23(43.4) | 2 (50)/2 (50) |
| Age at diagnosis, median (range) | 5 (0.2-17) | 5 (0.2-17) | 4.5 (1.5-7) |
| < 11 years | 40 (70.2) | 36 (67.9) | 4 (100) |
| ≥11 years | 17 (29.8) | 17 (32.1) | 0 |
| Previous infection | 11 (19.3) | 10 (18.9) | 1 (25) |
| Recent vaccination | 2 (3.5) | 2 (3.8) | 0 |
| Platelet count, median (range) | 11 (0-95x10$^9$/L) | 11.5 (0-95x10$^9$/L) | 11(6-59x10$^9$/L) |
| Acute onset | 34 (59.6) | 31 (58.5) | 3(75) |
| Insidious onset | 7 (12.3) | 6 (11.3) | 1(25) |
| Asymptomatic | 16 (28.1) | 16 (30.2) | 0 |
| Relapses | 6 (10.5) | 2 (3.8) | 4(100) |
| Follow-up, ongoing/complete/incomplete | 6 (10.5)/24 (42.1)/27 (47.4) | 6 (11.3)/24(45.3)/23 (43.4) | 0/0/4(100) |

*Except for the characteristics that indicate measurement by median and range

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## Discussion

Primary immune thrombocytopenia is an autoimmune disorder characterized by low platelet count due to premature platelet destruction and an impaired platelet production. In the present study, male gender was more common, which is consistent with other studies.[12] The average age was 6.8±4.2 years at the time of diagnosis, similar to that mentioned by Yong et al.[4] History of prior infection to the onset of hemorrhage was observed in 19.3% cases, lower than reported by other authors where it ranged from 46 to 57%.[12–14] A failure to inquire about history of infectious diseases or omission to report it in the patients' medical histories may explain this finding. Similarly, there were only two cases linked to the MMR vaccine, less than that reported by Ramyar et al; this contrast can be due to the fact that our study included patients up to 16 years of age, but Ramyar´s study only included infant patients. 15 Also, since the data in this study was acquired from a single hospital; potential bias may be to blame for differences with more sizeable or multicentric studies which were used to compare our findings.

Acute mucocutaneous hemorrhage, predominantly petechiae and ecchymosis, was the most common type of presentation, similar to that observed in other cohorts.[12,13,15,16] Only one patient presented menorrhagia as a sign of PIT, which is an uncommon manifestation, as suggested by Camacho et al.[17] Thrombocytopenia was an incidental finding in laboratory studies in almost a third of patients in this study. It has been calculated that 28% of patients with PIT are asymptomatic, thus diagnosis occurs through tests made for other causes. It has also been established that platelet count does not correlate to symptom occurrence.[3,18] Regarding treatment, therapeutic options varied greatly between patients; the majority of patients did not require pharmacological treatment, and IVIg was the most used treatment, followed by steroids.

Additionally, 12.3% received blood transfusions, more than double than what was described by Bennett et al.,[19] yet less than what is reported in Mexico.[16,19] Since the MCPG hasn't been updated since 2009, blood transfusions, among other aggressive therapies, are still recommended as an option to treat PIT manifestations, which can justify the higher rates of transfusions among Mexican patients. Still, an effort to use newer and updated guidelines has been established in the hematology department in the hospital. Responses were measured based on the first laboratory control, which was taken according to the individual characteristics of each patient. [20] Platelet count response of ≥100×109/L was observed at a median of 5 weeks, at least three weeks less than the study by Cooper et al., who recorded a median of 8 weeks (1 to 40 weeks).[21] A small percentage of patients developed chronic TIP, despite the natural history of the disease, which states that 13 to 36% will develop a chronic, refractory, and difficult to control form.[22] This is a low frequency, compared with similar international and national studies.[12–14,16,19] Only one of these patients had an insidious onset (risk factor for chronicity) and that same patient was the only one with a history of infection (protective factor); 75% of them received therapies recommended by the MCPG. The stepped care treatment that current guidelines advice, and is implemented in their management, may play a role in chronicity decrease.

Nonetheless, further studies in our hospital, or similar study populations, need to be done in order to properly identify associated factors, such as comparing outcomes according to the therapeutic regimes they underwent.

There were no severe complications or deaths associated with PIT diagnosis; another Mexican study also reported a lack of complications and deaths among their patients, which speculated that timely diagnosis and treatment decrease negative outcomes.[12] Bennet et al.,[19] lost 46.3% of their patients during the 12-month follow-up, which coincides with our results, since the abandonment rate within the study population was 47.4%. Lack of symptoms or concern may cause the patients' parents to abandon or refuse further consultations.

## Conclusion

Primary immune thrombocytopenia is the most frequent hematological disease pediatric patients that attend the Gyneco-Obstetrics and Pediatric Hospital No. 31. The majority of clinical and laboratory characteristics of the patients are in accordance with other national studies and international literature; the main clinical manifestation was mucocutaneous hemorrhage and thrombocytopenia tended to be very severe. A remarkable finding was the low frequency of chronic PIT. Differences in treatment approach between Mexican and American guidelines might explain the different patient outcomes.

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## Conflicts of interest

The authors declared there is no conflict of interest.

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