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Case Report

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Primary Immune Thrombopenia in Adults: About 55 Cases

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Abstract

Introduction: *ITP is an autoimmune cytopenia common in adults. The hemorrhagic risk may involve a vital prognosis. Its management is still poorly codified.*

We studied the diagnostic characteristics of ITP and evaluated its therapeutic management and its evolutionary profile in adults.

Materials and Methods: *this is a retrospective study of 55 cases of ITP, conducted over 21 years (January 2000 to December 2020).*

Results: *The average age of patients was 44 years with a clear female predominance (sex ratio 3.5). The circumstance of discovery was fortuitous in 41.8% of cases and following hemorrhagic syndrome in 34.5% of cases. Deep thrombocytopenia (< 30,000 el/mm3) was found in 42.8% of cases. The presence of bleeding was correlated with the depth of thrombocytopenia. Antinuclear antibodies were positive in 76% of cases. Corticosteroid therapy was prescribed first-line in 50.9% of patients. A response was obtained in 78.6% of cases. Splenectomy was performed in 12.7% of cases. The response rate was 57.1%. Four patients benefited from rituximab with an initial response observed in all cases. The trend towards chronicity was observed in 78.2% of cases.*

Conclusion: *ITP is a diagnosis of exclusion. It is mostly moving towards chronicity. Treatment is mainly based on corticosteroid therapy. Surveillance may be sufficient in the presence of hemostatic platelets. Splenectomy keeps room but is increasingly delayed after the advent of new therapies.*

Keywords: Thrombocytopenic Purpura, Immunological Thrombocytopenia, Corticosteroid Therapy.

1. Introduction

Primary immunologic thrombocytopenia (ITP) is a benign blood disorder [1]. It is the most common autoimmune cytopenia in adults [2]. Its clinical presentation is variable, ranging from a mostly asymptomatic character to the presence of various manifestations (petechial purpura, ecchymoses, hematomas, hemorrhages, etc.) with an increased risk of benign to life-threatening hemorrhages [3]. The history of the disease is most often intermittent, with remissions interspersed with more or less sudden and severe relapses. ITP is essentially a therapeutic problem because of the frequency of relapses, cortico-dependent and refractory forms. Currently, the therapeutic strategy for this disease is based on expert agreements; however, it remains non-consensual.

We studied the different epidemiological, clinical, biological, therapeutic, and evolutionary aspects of ITP in adults.

2. Patients and Methods

We conducted a single-center retrospective observational study. We studied 55 observations of patients with ITP, collected in the internal medicine department of the Hédi Chaker university hospital of Sfax during the period from January 2000 to December 2020 discovery in adulthood.

We included patients aged at least 16 years, whose ITP diagnosis met the standardization criteria of the 2009 expert conference and the 2017 recommendations of the French national protocol of diagnosis and care (PNDS), i.e. isolated thrombocytopenia at

diagnosis <100,000 el/mm3 and after elimination of other causes of thrombocytopenia. These patients were followed regularly at the inpatient and/or consultation department.

We excluded patients with secondary immunological thrombocytopenia (connective tissue disease, APS, primary immune deficiency, chronic infection, lymphoproliferative disease, autoimmune hemolytic anemia (EVANS syndrome), and drug-induced causes).

We analyzed the epidemiological, clinical, paraclinical, and evolutionary data. We evaluated the hemorrhagic syndrome using the Khellaf hemorrhagic score.

We identified four evolutionary modalities according to the response to the treatment, which we defined as follows:
• Complete response (CR): platelets above 100,000 el/mm3 and no bleeding)
• Partial response (PR): platelets between 30,000 - 100,000 el/mm3 and no bleeding
• Non-response (NR): platelets below 30,000 el/mm3 or platelets between 30,000 and 100,000 el/mm3 with bleeding
• Relapse (R): platelets below 30,000 el/mm3; or platelets between 30,000 and 100,000 el/mm3 with bleeding, after partial or complete response. For each relapse (if any): we specified the time between relapses, the cause of the relapse if any, occurring under which treatment and therapy used during the relapse, and the evolution after treatment.

We defined refractory ITP by the presence of relapse after splenectomy with severe ITP and a persistent bleeding risk.

3. Results

3.1 Epidemiological and Clinical Study

The mean age of our patients was 44 years with extremes ranging from 18 to 75 years? The peak frequency was in patients in their 40s (25%). There was a clear female predominance with a sex ratio of 3.5.

Thrombocytopenia was mostly discovered incidentally in 41.8% of cases. A hemorrhagic syndrome was found in 34.5% of cases.

Table 1: Different Types of Bleeding Syndromes in ITP

Type of bleeding syndrome		Number of cases (%)
Cutaneous hemorrhage	Petechial purpura	4 cases (7.3%)
	ecchymoses	13 cases (23.6%)
	Petechiae and ecchymoses	2 cases (4.7%)
Mucosal hemorrhage	Epistaxis	6 cases (10.9%)
	Gingivorrhages	8 cases (14.5%)
Visceral hemorrhage	Gynecological bleeding	6 cases (10.9%)

4. Biological Study

4.1 Blood Count

The initial platelet count ranged from 2000 to 100,000 el/mm3 with a median of 40,000/mm3 (IQR [9,500 - 70,000 el/mm3]).

Twenty-one patients (42.8%) had profound thrombocytopenia ≤ 30,000 el/mm3 including 16 patients (32.6%) with major thrombocytopenia ≤ 15,000 el/mm3 - Relationship between thrombocytopenia and hemorrhagic syndrome.

Nineteen cases had bleeding syndrome at initial diagnosis. They all had thrombocytopenia < 80,000 el/mm3 of which 14 patients (73.6% of cases) had platelet counts < 30,000 el/mm3.

Among 21 patients with deep thrombocytopenia, 14 (66.7% of cases) had a bleeding syndrome at diagnosis. The depth of thrombocytopenia was statistically associated with the bleeding syndrome (73.7% vs 26.3%; p = 0.001).

On the results of the hemogram, the hemoglobin level ranged from 6.7 to 17g/dl. The median was 13 g/dl (IQR [12.2 and 13.7. g/dl]). There were 10 cases of anemia (18.2%). All were women. The anemia was by iron deficiency in all cases.

5. Myelogram

Myelogram was performed in 47 patients (85.5% of cases). The peripheral origin of thrombocytopenia was retained in all cases.

6. Anti-Nuclear Antibodies

The search for anti-nuclear antibodies (ANA) was performed in all our patients. They were positive in 76.4% of cases (42 patients). The most frequent ANA titre found in our series was (1/160) in 33.3% of cases.

7. Treatment

In our series, 47.3% of patients (26 cases) received regular monitoring without the use of drugs at diagnosis. Twenty-three patients who received no treatment (88.4%) progressed favorably without relapse after a mean follow-up of 35 months. Only four patients (15.3% of all monitored patients) resorted to treatment after monitoring failure.

Corticosteroid therapy (CT) was used during management (initial and relapse) in 33 patients (60% of cases). The drug used was prednisone. High-dose CT (1 mg/ kg/day) was prescribed in 32 patients (58.2% of cases) with a duration of attack between 2 and 8 weeks. Bolus solumedrol (1g/d 3 days in a row) was used in four patients (7.3% of cases) in severe forms with major hemorrhage and/or major thrombocytopenia.

CT was used as first-line treatment in 52.7% of cases (29 patients). In four patients, CT was used as second-line treatment after the therapeutic failure of first-line monitoring.

Response judgment was based on platelet count after first-line CT, the mean of which was 91,900 el/mm3 (range 4,000 and 202,000 el/mm3).

A response was obtained in 22 patients (78.6% of the cases have received a CT with 1st intention). Eleven cases (39.3%) had a partial response and 11 cases (39.3%) had a complete response. Six patients had no response.

Among the 22 responders to first-line CT, nine had experienced at least one relapse. These were relapses following:
• A partial response in six cases (21.4% of patients treated with first-line CT).
• A complete response in three cases (10.7% of patients treated with CT in the first line)
• Among the 33 patients who received CT, 18 had a failure (5 cases) or a relapse (13 cases) after this first-line CT.

Among the 55 patients studied, four cases (7.3%) had received intravenous immunoglobulin (IVIG) treatment. The infusion regimen used was 1 g/kg/d of IVIG on Day 1 and repeated on Day 2. Only three patients showed a transient response. This treatment was prescribed as a third-line treatment in 2 patients (one case of refractory ITP and one case of coticoresistant ITP) and peripartum in 2 patients.

Treatments such as cyclophosphamide, Danazol, and vincristine were tried in one case each without satisfactory response.

Plaquenil was used in 6 patients, all of whom were ANA positive. A response was obtained in 5 patients who subsequently relapsed.

In our series, splenectomy was performed in 7 patients (12.7%). It was used as a second line (5 cases) or a third line (2 cases). The delay of splenectomy from the diagnosis of ITP had a median of 12 months (IQR [7 -24]). We achieved two CRs, without subsequent relapse. Three cases had PR: two cases had relapses at 1 month and 3 years, respectively. The other case had no relapse after a 2-year follow-up. Two cases had failed splenectomy. There was one case of splenectomy complicated by portal thrombosis.

Rituximab-based biotherapy was prescribed in four patients at a dose of 375mg/m2/cure in four weekly courses. This treatment was used in the second line in one patient, after a delay of 1 month of a CTFD associated with IVIG, without response, and in the third line in the three other cases. The indications were corticoresistant ITP for two patients and refractory ITP for the other two. One patient had received an incomplete protocol (the lost sight of after the third weekly treatment without a response). She presented a relapse of her disease 7 years later.

8. Evolution

In our series, we have six cases (10.9%) of acute ITP and 6 cases (10.9%) of persistent ITP. Forty-three patients (78.2%) developed chronic ITP.

We studied several predictive factors for progression to chronicity which were: female gender, initial platelet count ≤ 30,000 el/mm3, initial platelet count [30,000 - 100,000 el/mm3], presence of bleeding syndrome at initial diagnosis, and non-response to 1st line CT. Statistically, all these factors do not predict the transition of ITP to chronicity ($p > 0.05$) in our population.

9. Discussion

9.1 Epidemiological and Clinical Aspects

ITP is the most common autoimmune cytopenia in adults. About 15 studies, mostly conducted in Europe, have aimed to measure the incidence of ITP. The annual incidence estimates vary between 1.6 and 3.9 per 105 inhabitants in adults. These large differences in estimates are due to methodological differences in the definition and identification of patients between series [4].

In Europe, the majority of series (in France, the United Kingdom, Turkey, etc.) report a peak incidence of ITP in adults over 60 years of age [5,6]. In contrast, to the data of the North African series consulted (series by Belhaj et al Jaouhari et al [7,8], it seems that the peak incidence exists in young adults and elderly subjects are much less affected. The average age in our series was 44 years, and the peak frequency was observed in adults in their forties, which is consistent with the North African series. Indeed, like any autoimmune disease, the incidence of ITP differs according to the ethnic and geographical origin of the population studied [9].

According to the literature, the sex ratio is generally around 1.5 with a female predominance [10]. In our series, we also noted a predominance of females with an F/H sex ratio of 3.5, which is higher than in the literature.
Thrombocytopenia in ITP may be discovered incidentally in 11 to 35% of cases [11]. The bleeding syndrome is the most frequent circumstance of discovery according to the majority of published series, accounting for up to 89% of cases [12]. Different types of bleeding syndromes can be observed, ranging from the least severe to serious forms involving the vital prognosis.

Cutaneous bleeding was the most frequent manifestation in all series consulted as well as in our series, followed by mucosal and visceral bleeding. Table 2 summarizes the circumstances of ITP findings most reported in the literature and in our series.

Table 2 : Circumstances of Discovery of ITP

Series	Discovery mode					
	Number of cases	Incidental finding %	Bleeding %	Type of bleeding %		
				Cutaneous	Mucosal	Visceral
***S. Audia et al* [12]**	40	35	65	45	22.5	2.5
***B. Bennani et al* [11]**	42	11	89	76.1	71.4	42.8
***G.E. Pamuk et al* [13]**	321	--	73.2	30.1	11.5	--
***Belhaj et al* [7]**	169	17	83	87	76	16
Our series	55	41.8	34.5	25.6	25.4	10.9

To quantify the hemorrhagic syndrome of patients, we used the Khellaf hemorrhagic score. This score is used to guide the therapeutic management of the patient [13,14].

In the literature, a difference in the presentation of hemorrhagic symptoms with age and sex was noted but without statistical significance [15]. However, Piel-Julian et al reported that the female gender was associated with a higher risk of bleeding with an OR of 2.58 (1.33 - 5.01) and that advanced age (>80 years) was correlated with the severity of the bleeding syndrome (OR 2.53 (1.01-6.35)) [16]. We did not find a correlation in our series.

10. Biological Aspects

The blood count is the key test to detect thrombocytopenia as well as any qualitative and/or quantitative abnormalities in other bloodlines that would point to central thrombocytopenia [17].

Usually, in ITP, thrombocytopenia is profound. In our series, the platelet count at diagnosis had a median of 40,000 el/mm3 (IQR [9,500 - 70,000 el/mm3]). Almost half had profound thrombocytopenia (≤ 30,000 el/mm3) and one-third had major thrombocytopenia (≤ 15,000 el/mm3).

It has been shown through the majority of published series that the deeper the thrombocytopenia, the greater the risk of developing a bleeding syndrome Thrombocytopenia ≤ 20,000 el/mm3 is identified by several studies as a predictive factor for major bleeding [18]. In our study, the depth of thrombocytopenia was statistically associated with the bleeding syndrome (73.7% VS 26.3%; p = 0.001).

Iron deficiency anemia secondary to bleeding may be associated with thrombocytopenia in ITP [19]. It affects women preferentially and this could be explained by menstrual bleeding aggravated by thrombocytopenia which is the case for 18.2% of our patients, all of whom were female.

The performance of the myelogram is the subject of controversy. Some authors recommend not performing the myelogram in patients with typical ITP even after the age of 60 years [20]. However, others suggest that myelograms should be performed in all patients followed for ITP [21]. The 2011 and 2019 American Society of Hematology (ASH) recommendations, the 2010 International Consensus Report on the Investigation and Management of ITP updated in 2019, and the 2017 NDSP suggest that myelogram is essential in specific situations such as age greater than 60 years, presence of organomegaly, presence of abnormalities in other lineages, and lack of response to first-line therapy and before splenectomy [22]. We believe that the myelogram should be performed routinely in any patient with persistent thrombocytopenia to avoid missing certain diagnoses and in particular infiltrative diseases.

As part of the etiological workup, ANA positivity is considered a predictive factor for chronicity in children [23]. However, this remains debated in adults [24]. However, the SAH (2019) does not recommend routine testing for ANAs . The rate of ANA positivity during ITP in adults varied according to the series from 7% to 76.3% (Table 3).

Table 3 : Ana Positivity Rates in Different Series

Series	Performed in % of cases	% ANA positivity	Positivity threshold
Altintas et al [23]	100	33.3	1/80
Moulis et al [24]	77.3	42.8	1/160
Belhaj et al [7]	68	7	1/80
Our series	100	76.3	1/80
ANA: antinuclear antibodies			

The high rate of positive ANAs in our series is due to selection bias (the majority of our patients were referred to our department from the clinical hematology department for positive ANAs).

11. Treatment

Treatment aims to achieve a "safe" platelet threshold specific to each patient to avoid a bleeding event. Its ultimate goal is the arrest of major bleeding in relapse events and the prevention of subsequent bleeding episodes.

A suggested platelet count ≥ 20,000 - 30,000 el/mm3, without the need for normalization, because a platelet count below this threshold increases the risk of bleeding. The treatment must have minimal toxicity. All drugs should be avoided in asymptomatic patients with moderate thrombocytopenia. In our series, abstention combined with clinical and biological monitoring was the therapeutic alternative of choice in about half of the cases.

Schematically, treatment is indicated when the platelet count is < 30,000 el/mm3, especially if there are signs of bleeding. This threshold may be increased in situations where the risk of bleeding is increased (elderly subjects, comorbidity, concomitant use of drugs that interfere with hemostasis, pregnancy, sports, or professional activities with a risk of trauma).

Corticosteroid therapy is the cornerstone in the treatment of ITP. The most commonly used glucocorticoids are prednisone, prednisolone, methylprednisolone, and dexamethasone. Methylprednisolone is prescribed intravenously. It is proposed in case of a major bleeding syndrome at a dose of 15 mg/kg/day, not exceeding 1g on Day 1, possibly repeated on Days 2 and 3. It is effective in more than 80% of cases, but with a transient effect.
High-dose CT is used for 3 to 4 weeks with a gradual decrease until it is stopped. It is prescribed as a starting dose of CT or as a follow-up to boluses of methylprednisolone. CT is appropriate for newly diagnosed ITP or relapses of persistent or chronic ITP.

The duration of CT is increasingly shortened (≤ 6 weeks), All recommendations (from the SAH (2019), the 2017 PNDS, and the 2009 international consensus updated in 2019) currently recognize the impertinence of prolonged corticosteroid therapy beyond 6 weeks (maximum of 8 weeks).
For patients requiring additional treatment, alternative therapy should be considered rather than continuous exposure to corticosteroids.

The prolonged duration of CT only increases the risk of occurrence of side effects without having a real gain in terms of efficacy in the treatment of ITP.

In the 2019 international consensus recommendations and the 2017 NDPDS, resumption of corticosteroid therapy is not included in relapse situations or as 2nd-line treatment. However, intravenous CT may be initiated to achieve a temporary response in cases of major trauma or surgery in patients with refractory ITP [25].

IVIg has been shown to produce a short-term response rate of nearly 90%, but relapse within 2 to 4 weeks was almost inevitable [26]. The latest recommendations call for a dose of 1 to 2 g/kg over 1 or 2 consecutive days or 0.4 g/kg/d for 5 days, with the possibility of repeating the treatment depending on the platelet response according to some authors [27].

The SAH (2019) places splenectomy as a second-line treatment in conjunction with thrombopoietin receptor agonists (TPO-RA) and rituximab. The choice will be for chronic corticosteroid-dependent ITP based on patient preference and goals.

It is important to avoid this radical and aggressive treatment for the first year after the diagnosis of ITP; complete remission or even spontaneous cure or cure with first-line therapy is possible [27]. In 80-90% of ITP patients, platelet counts increase immediately after splenectomy and 50%-70% of patients achieve durable remission [28].

Rituximab was first used in chronic ITP in 2001 by Stasi et al with promising results (52% overall response rate) and has been widely used as a second or third-line therapy for the treatment of persistent and chronic ITP [29]. This has allowed us to gain insight into the efficacy and safety of this molecule in the management of ITP [30]. This treatment, used at a rate of 4 weekly infusions of 375 mg/m2, allows a satisfactory response rate to be obtained for ITP (overall 60% of immediate responses and 30 to 40% of prolonged responses) [31]. Two injections 14 days apart of a fixed dose of 1 g independent of weight were also effective and well tolerated.

Fostamatinib is an inhibitor of phagocytosis by inhibiting spleen tyrosine kinase (SYK) [32]. It was approved by the 2019 International Consensus Report with a robust level of evidence for the treatment of adults with chronic ITP refractory to prior therapies. This treatment was not used in our series.

TPO-RAs are a relatively new therapeutic approach as all other treatments target the autoimmune phenomenon of platelet destruction [33]. The molecules currently available and which have marketing authorization in Europe and America are eltrombopag (Revolade®), romiplostim (Nplate®), and avatrombopag . The response rate varies between 50% and 90%. Approximately 10 to 30% of patients on OPT-AR will be able to stop their treatment and maintain the response after stopping. The safety profile of these molecules is good in the short and medium term. None of our patients has received these drugs.

Some therapeutics are in the advanced phase of clinical trials (phase III) and seem to give good results that could enrich the therapeutic arsenal of ITP in the coming years. We mention: Rozanolixizumab, Rozrolimupab, PRTX-100, BTK-inhibitors, FCRN-inhibitors, belimumab... [34].

12. Evolution

ITP can be classified into three periods according to the duration of evolution Acute or newly diagnosed ITP is the initial phase of the disease. The chance of recovery during this period remains possible. In a prospective multicenter study conducted in southern France in 2017 involving 90 cases of acute ITP (CARMEN registry), 31.8% had a CR at 3 months of the evolution of which 32.1% never received treatment. In persistent ITP, during which it is impossible to predict the future course of the disease, a complete remission or even a spontaneous cure or after first-line treatment remains possible in 20 to 30% of cases, thus avoiding the use of radical and aggressive treatments, in particular splenectomy, during the first year following the diagnosis. Chronic ITP is the most frequent evolutionary mode. More than 60% of patients have an evolution of more than 1 year, after which spontaneous cures are rare (less than 5%).

According to the 2017 PNDS, the most commonly identified predictors of chronicity are absent or insidious hemorrhagic symptomatology at initial diagnosis and a moderately lowered platelet count. However, in a prospective multicenter study of 188 cases, it was concluded that initial moderate thrombocytopenia did not correlate with a high risk of progression to chronicity, as did NAA positivity, age, sex, and bleeding symptomatology [35]. In another multicenter study in southern France, NAA positivity was reported as a predictive factor for progression to chronicity. Therefore, there are no risk factors for progression to chronicity with great certainty.

13. Conclusion

Despite the retrospective nature of this study including a relatively small number of ITP patients and the selection of a good proportion of patients referred for ITP with positive ANAs, our results are close to those reported in the literature. This positivity does not call into question the diagnosis and does not modify the evolutionary course of the disease.

A better understanding of the pathophysiology of ITP has led to the development of new treatments. Progress in this field will likely revolutionize the management strategy for this disease, which has a definite impact on patient's quality of life. New therapeutic approaches, in targeted therapy molecules, are being developed with very promising results.

14. Conflict of Interest Disclosure

The Authors Declare That There Are Not Conflicts Of Interest

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