

## CLINICO HEMATOLOGIC FEATURES OF IMMUNE THROMBOCYTOPENIC PURPURA AND ITS ASSOCIATION WITH AUTOIMMUNE DISORDERS.

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### ABSTRACT

*Immune thrombocytopenic purpura (ITP) is a clinical syndrome in which a decreased number of circulating platelets (thrombocytopenia) manifests as a bleeding tendency, easy bruising (purpura), or extravasation of blood from capillaries into skin and mucous membranes (petechiae). Present study was done to observe the clinico-haematological features of ITP in Adults and to analyse the association of autoimmune disorders with ITP in Pakistani patients. It was a cross-sectional descriptive study conducted at Shaikh Zayed Hospital, Lahore, from 1st January 2006 to 30<sup>th</sup> June 2007. The study included 44 adult patients of both genders diagnosed as having ITP according to WHO guidelines. Bone marrow biopsy was carried out in all patients and other causes of thrombocytopenia were carefully excluded. Antinuclear antibodies, rheumatoid factor, HBs Ag, anti HCV, HIV were also done. The data was analysed by SPSS version 10. Results showed peak incidence in third decade with female to male ratio of 3.1:. Bleeding and bruising were common symptoms of ITP. Seven (15.9%) of 44 patients had serological evidence of systemic autoimmune disorders, i.e., SLE or RA. Platelet count was significantly lower in SLE patients than in entire cohort. It was concluded that adult ITP is predominantly seen in young females, presents with bleeding from more than 2 sites and may be associated with autoimmune disorders at the time of diagnosis.*

**Key words:** *Immune thrombocytopenic purpura. Autoimmune disorders.*

### INTRODUCTION

Idiopathic thrombocytopenic purpura (ITP) is an acquired haemorrhagic disorder characterized by thrombocytopenia that is defined as a platelet count less than  $150 \times 10^9/L$  (150,000/ul), a purpuric rash, normal bone marrow, and the absence of signs of other identifiable causes of thrombocytopenia<sup>1</sup>. In 1735 ITP was described by Werlhof as morbus maculosus haemorrhagicus<sup>2</sup>. In 1883 Kraus observed decreased platelets on the blood smear of affected patients. In 1916 splenectomy of an affected woman increased platelets from 2k to 500k. Finally in 1951 the simple observation that normal people transfused with plasma of ITP patients had rapid decrease in platelets, led the scientists to look for a transferrable aetiological agent like antibody<sup>3</sup>. Both the American Society of Haematology<sup>4</sup> and the British Committee for Standards in Haematology, General Haematology Task Force have issued “practice guidelines.”

ITP is classified as acute or chronic, with the latter defined as the persistence of thrombocytopenia for more than 6 months from the initial presentation of signs and symptoms. ITP is estimated to be one of the most common acquired bleeding disorders encountered by paediatricians,

with the incidence of symptomatic disease being approximately 3 to 8 per 100,000 children per year. Acute ITP is more prevalent among children younger than 10 years of age, affects males and females equally, and is more prevalent during the late winter and spring. Chronic ITP affects adolescents more often than younger children, with females being affected more frequently than males. Unlike acute ITP, it does not show a seasonal predilection<sup>1</sup>. In persons with ITP, platelets are coated with autoantibodies to platelet membrane antigens, resulting in splenic sequestration and phagocytosis by mononuclear macrophages. The resulting shortened life span of platelets in the circulation, together with incomplete compensation by increased platelet production by bone marrow megakaryocytes, results in a decreased platelet count<sup>5</sup>. Patients who have chronic ITP are more likely to exhibit an underlying autoimmune disorder, with up to one third having clinical and laboratory manifestations of collagen-vascular disease.<sup>6-8</sup>

The present study was designed to observe the clinic-haematological features of ITP in adults and to describe the associated factors of ITP especially autoimmune disorders in Pakistani patients.

**PATIENTS & METHODS:**

This study included 44 adult (>15 yrs) patients of both genders diagnosed as having ITP on the history, physical examination, complete blood count, examination of the peripheral smear and bone marrow biopsy.

Patients with other causes of thrombocytopaenia (inherited thrombocytopaenias, bone marrow failure syndromes, lympho/myelo proliferative disorders and thrombotic microangiopathies, megaloblastic anaemias and pseudothrombocytopaenia) were carefully excluded according to the findings in history, physical examination and investigations. Patients with history of chemo/radiotherapy and interferon therapy during last 6 months were also excluded.

This study was performed in one and a half year i.e. from 1st January 2006 to 30th June 2007.

**Data Collection Technique**

A total of 44 patients were included in the study. Informed consent was obtained and in all of them important presenting complaints, findings on physical examination and investigations were recorded as performed on Sysmax KX-21 automatic haematological analyser. Manual platelet count was also carried out using a Neubaur chamber. Auto-immune profile (ANA, RA factor) was also performed using latex agglutination method. Diagnoses of SLE and RA were based on clinical and serological data. Serology of HBs Ag and Anti-HCV were done with ELISA. HIV testing was performed with chromatographic technique.

**Data Analysis**

All the data was entered into SPSS version 10 for analysis. Quantitative variables were expressed as mean, median and standard deviation. Qualitative variables were described as frequencies and percentages. Different aetiological or associated factors were analysed and their association with ITP was analysed (by chi square) for any statistical significance. Mean laboratory parameters (Hb, TLC, Platelet count) were compared in patients with SLE, RA and in entire cohort. P value 0.05 was considered as statistically significant.

**RESULTS**

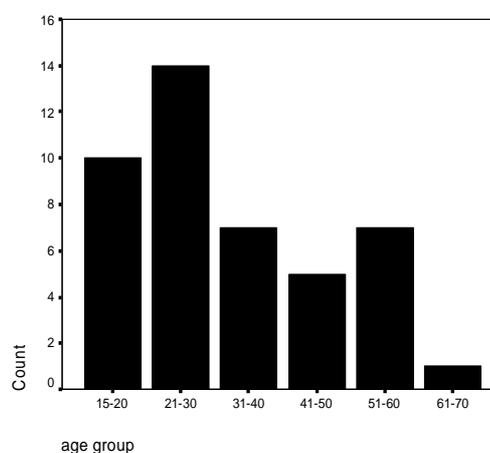
The study was performed over a period of one and a half year. During the period of this study 44 adult patients were diagnosed as ITP.

Mean age of the patients in the study was 33.9 ± 14.1 years. (Median age 30 years). Majority of the patients were in a younger age group (<40 years). Peak incidence was in third decade. There was a female predominance, with 11 (25%) males and 33 (75%) females. Female to male ratio was

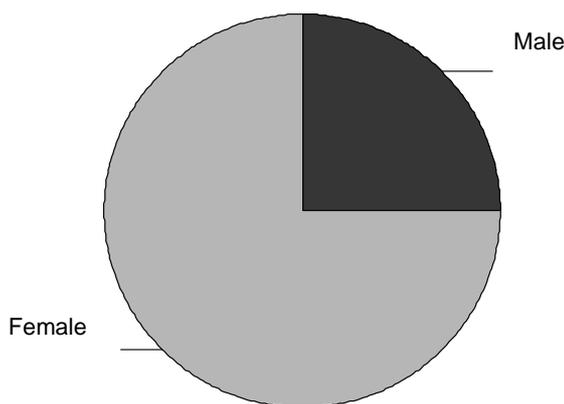
3:1. All patients with autoimmune disorders were females and their mean age was 22 years.

**Table 1:** Different signs and symptoms in 44 adult ITP patients at presentation.

Sr. No.	Signs & Symptoms	Frequency (Percentage)
1.	Bleeding 2 sites	38 (86%)
2.	Bruising	35 (79%)
3.	Hepatomegaly	10 (22%)
4.	Splenomegaly	11 (25%)
5.	Lymph-adenopathy	03 (6.8%)



**Fig. 1:** Analysis of different age groups in 44 adult ITP patients.



**Fig. 2:** Male and female distribution in 44 adult ITP patients.

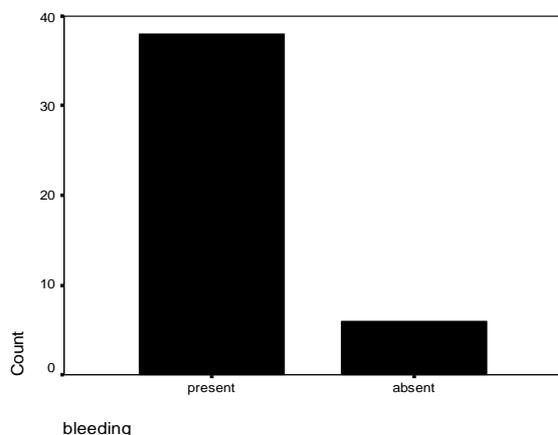
Different signs and symptoms included bleeding, bruising and hepato/splenomegaly. Bleeding from more than one site was present in 38 (86.4%) patients. Bruising was present in 35 (79.5%) pati-

ents. Liver was palpable in 10 (22.7%) patients while splenomegaly was found in 11 (25%) patients. It was observed that majority of the patients with hepatic and/or splenic enlargement were hepatitis C positive. Palpable lymph nodes were present in 3 (6.8%) patients only (Table 1).

Different laboratory parameters were analysed in all the patients. Mean Hb was 10.6 g/dl  $\pm$  2.8. Mean TLC was  $8.5 \times 10^3/\text{ul} \pm 4$ . Mean platelet count was  $12 \times 10^3/\text{ul}$  with range from 0 –  $31 \times 10^3/\text{ul}$ . Mean PT was 17 sec (control 13 sec) and mean APTT was 38 sec (control 30 sec). Prolonged PT and APTT were seen mostly in Hepatitis B and C positive cases (Table 2).

**Table 3:** Association factors in 44 adult ITP patients.

Sr. No.	Association Factors	Present in N (%)
1.	SLE	5 (11.4%)
2.	RA	2 (4.6 %)
3.	Hepatitis B	2 (4.5%)
4.	Hepatitis C	10 (22.7%)
5.	HIV	0



**Fig. 3:** Presence of bleeding from >1 sites in 44 adult ITP patients.

**Table 2:** Haematologic parameters in 44 adult ITP patients.

Sr No.	Haematologic parameter	Mean $\pm$ SD	Median	Range	Reference value
1.	Haemoglobin (g/dl)	10.6 $\pm$ 2.8	11	5 – 17.8	11.5 – 17 g/dl
2.	Total Leukocyte Count ( $\times 10^3/\text{ul}$ )	8.5 $\pm$ 4.0	7.6	3.5 – 22	4 – 11 $\times 10^3/\text{ul}$
3.	Platelet count ( $\times 10^3/\text{ul}$ )	12 $\pm$ 19	5	0 – 31	150-400 $\times 10^3/\text{ul}$
4.	PT (sec)	17 $\pm$ 11	14	10 – 58	12 sec
5.	APTT(sec)	38 $\pm$ 11.8	35	24 – 64	30 sec

Possible association of autoimmune disorders with ITP was looked for. In 7 patients autoimmune profile was positive. Five (11.4%) patients had SLE and 2 (4.5%) had rheumatoid arthritis (Table 3).

Different haematological parameters were analysed in patients who had autoimmune disorder as association factor and mean values were compared with those of entire cohort. There was no significant difference in haemoglobin and total leucocyte count in patients with SLE and RA as compared to entire cohort. Mean platelet count in patients with SLE was  $2.3 \times 10^3/\text{ul}$  (significantly lower than value in total ITP patients). In patients with RA, mean platelet count was  $10 \times 10^3/\text{ul}$  which was close to  $12 \times 10^3/\text{ul}$  seen in the entire cohort (Table 4).

## DISCUSSION

This study comprises of 44 patients, in whom 11 were males and 33 were female patients. Experience from numerous centers over the last 50 years indicates that the typical adult with ITP is a woman<sup>5</sup>, generally between 18 and 40 years of age.

The female - male ratio described earlier was 1.7:1<sup>1</sup>. In our study there was also a female predominance and mean age was 33 years. However the mean age in patients with auto-immune disorder was lower (22 years). It is reported in some studies that gender disparity largely disappears among the elderly.<sup>6,7</sup> However, some workers have questioned this perception. The first was a survey from a single county in Finland using International Classification of Disease (ICD) codes at hospital discharge over a 22-year period<sup>9</sup>. The female-male ratio was 1.7, the median age at diagnosis was 56 years, and the incidence of ITP increased with age and increased overall during the period of study.

The second was a prospective cohort analysis of newly presenting adults with platelet counts less than  $50 \times 10^3/\text{ul}$  in the Northern Health Region of the United Kingdom. The female-male ratio was

1.2 and, again, the age-specific incidence was highest among those older than 60 years.<sup>10</sup>

An association of ITP with autoimmune disorders was observed in the present study.

Seven patients (15.9%) in our study had serological evidence of autoimmune disorders at the time of diagnosis of ITP. Five (11.4%) patients were diagnosed as having systemic lupus erythematosus and 2 (4.5%) had rheumatoid arthritis. Wang<sup>11</sup> reported that 5-15% of patients with ITP fulfill the criteria for the diagnosis of SLE at the time of presentation. Approximately 3.6% patients with SLE developed ITP over 4 years<sup>11</sup>. Balsalobre et al<sup>12</sup> reported that many patients have a positive ANA test first time when they were diagnosed with ITP. All patients in their study were females, with a mean age of 32 at the time of ITP diagnosis and 36 at the time of SLE diagnosis<sup>12</sup>. The most usual clinical manifestations were: arthritis (92%), cutaneous (58%) and haematological involvement with lymphopaenia (58%) and thrombocytopenia again (33%) after the initial ITP episode, always together with autoimmune haemolytic anaemia (Evans syndrome). None of these patients presented with neurological involvement and only one presented with renal involvement. Among them 50% were positive for anti-DNA antibodies, 50% were Ro(+) and 16% were RNP (+). 66% were positive for anti-phospholipid antibodies and 33% for lupus anticoagulant.<sup>12</sup>

The development of ITP can precede the diagnosis of lupus by months to years<sup>13</sup> ITP can be the first manifestation of autoimmune disorder so it is important to include autoimmune serology in the initial workup of all patients of ITP. It has some prognostic implications as well. In a cohort of ITP patients with SLE, thrombocytopenia was controlled just with steroids in only 16% of the patients. Splenectomy controlled thrombocytopenia with complete remission achieved in 80% (4 of 5) of the patients and 20% (1 of 5) were refractory to this therapy after a medium follow-up time of 6.5 years.<sup>12</sup>

A recent study by Kuwana<sup>14</sup> et al shows that anti-GPIIb/IIIa and anti-TPOR antibodies are major factors contributing to SLE-associated thrombocytopenia. Anti-GPIIb/IIIa and anti-TPOR antibody responses were more frequent in SLE patients with thrombocytopenia than in those without thrombocytopenia (88 vs 17%,  $P < 0.0001$ ; and 22% vs 0%,  $P = 0.01$ , respectively). The frequencies of these platelet-related antibodies were

**Table 4:** Comparison of haematologic parameters in the presence of autoimmune disorders in 44 adult ITP patients.

Laboratory Parameter (Mean value)	ITP Cases N = 44	ITP+ RA N = 2	ITP+ SLE N = 5
Hemoglobin	10.6 g/dl	11 g/dl	10 g/dl
Total Leucocyte Count	$8.5 \times 10^3/\text{ul}$	$8 \times 10^3/\text{ul}$	$6 \times 10^3/\text{ul}$
Platelets	$12 \times 10^3/\text{ul}$	$10 \times 10^3/\text{ul}$	$2.3^* \times 10^3/\text{ul}$

Statistically significant p value\*

comparable between SLE patients with thrombocytopenia and patients with idiopathic thrombocytopenia. Twenty-nine (91%) SLE patients with thrombocytopenia had either anti-GPIIb/IIIa or anti-TPOR antibody, and six had both. In SLE patients with thrombocytopenia, the anti-TPOR-positive patients had significantly higher frequencies of megakaryocytic hypoplasia and poorer therapeutic responses to corticosteroids and intravenous immunoglobulin than did the anti-TPOR-negative patients, most of whom had the anti-GPIIb/IIIa antibody alone. In summary, measurement of anti-GPIIb/IIIa anti-TPOR antibody responses is useful in distinguishing between subsets of patients with SLE and thrombocytopenia and predicting their therapeutic response<sup>14</sup>.

In our study 2 (4.5%) of the patients with immune thrombocytopenia are associated with rheumatoid arthritis. In a study by Ichikawa et al<sup>15</sup> five cases of RA with ITP were reported. In all five patients, platelet counts were low, platelet-associated IgG levels were elevated, and bone marrow aspiration showed megakaryocytosis<sup>15</sup>.

Rheumatoid arthritis, in common with other systemic autoimmune diseases, can involve several other organs presenting with complex immunological manifestations. Immune thrombocytopenic purpura caused by an autoimmune reaction against platelets is an infrequent haematological complications.<sup>16</sup> Association of ITP with RA has been reported in the present study and in many case reports,<sup>16-18</sup> however it is less common than SLE. The combination of RA, ITP and Hashimoto's thyroiditis is extremely rare although these three disorders are classified as autoimmune disease<sup>18</sup>.

It is **concluded** that ITP is primarily a disease of increased peripheral platelet destruction, most patients are females. Adult ITP is frequently associated with systemic autoimmune disorders like SLE and rheumatoid arthritis.

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