ADULT IDIOPATHIC THROMBOCYTOPENIC PURPURA (ITP) – A PROSPECTIVE TRACKING OF ITS NATURAL HISTORY

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ABSTRACT

Thirty-seven Asian patients (30 women, 7 men) with chronic idiopathic thrombocytopenic purpura (ITP) followed prospectively for 4 to 15 years showed a highly variable clinical course. The women as a group had a much lower initial platelet count than the men (28 x 10^9/l versus 54 x 10^9/l). All the women but only 2 men required treatment for symptomatic thrombocytopenia. Six women developed secondary autoimmune disorders (4 systemic lupus erythematosus and 2 Evan's syndrome) after 14 to 33 months of clinical follow up. Although their responses to corticosteroid therapy were suboptimal when initiated for ITP, these 6 patients uniformly demonstrated a complete platelet response when corticosteroid treatment was re-introduced following the evolution of secondary autoimmune disorders. Four of the 5 untreated men were over 55 years of age. Their mild to moderate thrombocytopenia was discovered incidentally and they remained symptom-free after a follow up of at least 5 years. The overall response rates of this cohort of Asian patients to corticosteroid therapy and splenectomy are compared with those reported from the West. Three deaths are recorded in this study, one from intracranial haemorrhage and 2 gram negative septicaemia in steroid-dependent postsplenectomy patients.

The variable behaviour of this cohort of ITP patients emphasises the need for individualised management. Asymptomatic thrombocytopenia can be observed without treatment. Two fatalities from gram negative septicaemia in asplenic, steroid-dependent patients caution against the hasty recommendation of splenectomy for refractory ITP.

Keywords: *immune thrombocytopenia, secondary autoimmune disorders, gram negative septicaemia*

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INTRODUCTION

The purpose of this study is to determine if our Asian patients with chronic idiopathic thrombocytopenic purpura (ITP) behave differently from patients in the West. Thirty-seven local patients with chronic ITP followed for 4 to 15 years reveal a highly variable clinical course that suggests it may be a more heterogenous disorder than that encountered in the West.

MATERIALS AND METHODS

Chronic ITP is a clinical diagnosis based on the exhaustive exclusion of disorders and situations known to be associated with thrombocytopenia. The demonstration of the presence of antiplatelet antibody is not a pre-requisite for its diagnosis in Singapore because the methods in use here lack sensitivitiy and specificity. For inclusion in this study a patient must fulfill seven criteria at the initial assessment: (1) be 12 years of age or older, (2) no recent ingestion of drugs known to be associated with a reduced platelet count, (3) no hepatosplenomegaly or lymphadenopathy, (4) with at least two consecutive platelet counts < 130 x 10^9/l (the local normal range being 130 - 400 x 10^9/l), normal WBC and normal or near normal haemoglobin levels. Untreated, the thrombocytopenia persists for at least 6 weeks, thus distinguishing it from acute ITP. (5) No clinical or laboratory evidence of microangiopathy or disseminated intravascular coagulation (DIC), (6) normal to increased numbers of megakaryocytes on bone marrow aspirate or biopsy, (7) no clinical or serological evidence of a connective tissue disorder such as systemic lupus erythematosus (SLE) or rheumatoid arthritis. Since 1988 when cytogenetic analysis of bone marrow cells became feasible in this institution, a normal bone marrow karyotype is also a requirement for the diagnosis of ITP.

Patient Selection

Each thrombocytopenic patient was first clinically appraised to exclude the more obvious secondary causes of thrombocytopenia. A detailed history and careful physical examination served to exclude (1) a drug or an infection related cause, (2) a connective tissue disorder, (3) chronic liver disease with hypersplenism, (4) a neoplasm especially a lymphoid malignancy.

The typical ITP patient in this study was well but commonly experienced easy or spontaneous bruising and minor gum bleeding. The duration of symptoms prior to clinical evaluation varied between patients but the range was several weeks to many months. Physical signs were limited to petechiae and painless ecchymoses of the extremities, especially of the lower limbs. Patients with lymphadenopathy, hepatosplenomegaly or stigmata of chronic liver disease were excluded. If the size of the liver or spleen could not be determined clinically, then abdominal ultrasonography or computerised tomography was performed to rule out hepatosplenomegaly objectively. A normal chest radiograph showing the absence of hilar or mediastinal lymphadenopathy was required as well for patient inclusion.

Laboratory tests were performed to exclude platelet consumption (DIC screening and examination for RBC microangiopathic changes), immune haemolysis (direct Coombs' test), SLE (antinuclear antibody and anti-double stranded DNA antibody titres) and the anti-phospholipid syndrome (lupus anticoagulant and anticardiolipin antibody titres). A patient was excluded if any of these tests was positive. The rigorous process of selection resulted in 42 patients between 1978 and 1990 with the diagnosis of adult chronic ITP. Five patients defaulted within the first year of diagnosis and were excluded from the study. The remaining 37 patients have been followed-up for 4 to 15 years.

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RESULTS

The clinical profile of the 37 patients is summarised in Table I. The youngest patient was a 15-year-old Malay schoolgirl and the oldest was a 73-year-old Chinese man. The majority of the patients (75.6%) were in the third to sixth decade of life at diagnosis. The 5 patients lost to follow up in the first year of clinical contact were women. This gave a corrected male to female ratio of 1:5. The corrected racial distribution (Table I, in brackets) show no ethnic predilection.

Table I – Age, sex and racial distribution of patients with chronic ITP diagnosed between 1988 to 1990.

Patient characteristics	No. of patients	%
Age (in years)		
12 – 20	5	13.5 (11.9)
21 – 40	15 (plus 3)	40.5 (42.9)
41 – 61	13 (plus 2)	35.1 (35.7)
Above 60	4	10.9 (9.5)
Sex		
Female	30 (plus 5)	81.0 (83.2)
Male	7	19.0 (16.8)
Race		
Chinese	28 (plus 3)	75.7 (74.0)
Malay	5 (plus 2)	13.5 (16.6)
Indian	4	10.8 (9.4)

Note: The distribution of the five patients lost to follow up as well as the corrected percentages is given in brackets.

Thirty-two patients were symptomatic at presentation (Table II). Twenty-eight patients complained of easy or spontaneous bruising and minor mucosal bleeding, mainly from the gums. The platelet counts for this group of patients ranged from 10 x 10^9/l to 65 x 10^9/l. Four patients had major bleeding events either at presentation or during the initial assessment period. The range of platelet counts for these 4 patients during the haemorrhage was 5 x 10^9/l to 32 x 10^9/l. Three had gastrointestinal haemorrhage but a local cause was not identified on endoscopic examinations and one developed an intracerebral haematoma. The latter occurred in a 15-year-old Malay girl who was given both corticosteroid therapy and platelet concentrates and who made a full neurological recovery and subsequently completed her pre-university education and a diploma course at a polytechnical institute. She had multiple relapses in the 14 years of follow up, each readily remitted with short courses of intensified prednisolone therapy. The 3 patients who suffered gastrointestinal haemorrhage consisted of 2 young men below 30 years of age and a 62-year-old woman. Bleeding ceased within 72 hours of the commencement of corticosteroid treatment alone in the 2 young men but the elderly patient required in addition the infusion of multiple units of random platelet concentrates.

Table II – Initial presenting features of 37 patients with chronic ITP.

Presenting Features	Sex		Number of Patients
	Female	Male	
Asymptomatic	0	5	5
Minor bleeding	28	0	28
Major haemorrhage	2	2	4
Mean platelet count	28 x 10^9/l	54 x 10^9/l	

Five patients, all men, were asymptomatic at initial assessment. Their platelet counts ranged from 45 x 10^9/l to 110 x 10^9/l. The thrombocytopenia in each patient was incidentally discovered from a routine full blood cell count. The average follow up of this subgroup of patients was 6.5 years during which the platelet counts fluctuated between mild to moderate thrombocytopenia. One patient was 25 years of age but the other 4 were between 58 to 73 years old. The average age for this group of asymptomatic, mild chronic ITP was 56.6 years.

All the women received treatment either immediately for severe thrombocytopenia (platelet counts <20 x 10^9/l) or within several weeks of follow up because of cosmetically distressing recurrent ecchymoses associated with moderate thrombocytopenia (platelet counts of 20 x 10^9/l to 50 x 10^9/l). At presentation the mean platelet count for the women as a group was strikingly lower than that for the 7 men (28 x 10^9/l versus 54 x 10^9/l). Only 2 men required therapy, both had platelet counts <20 x 10^9/l and complicated by gastrointestinal haemorrhage without a local cause. The daily dose of prednisolone was 1 mg/kg body weight for severe thrombocytopenia and 0.25 to 0.5 mg/kg body weight for moderate thrombocytopenia. Table III summarises the response of the 32 patients. Twenty-four (75%) responded with 14 attaining normal platelet counts within 6 weeks of prednisolone treatment. A partial response was recorded for 10 patients whose platelet counts levelled out between 6 weeks to 3 months in a subnormal range of 30 x 10^9/l to 90 x 10^9/l. For both groups of responsive patients, once the maximum response was observed the dose of prednisolone was carefully reduced over 3 to 6 months to a maintenance daily dose of 10 mg or less. Among the 14 patients who responded completely, only one patient, the 62-year-old woman who presented with gastrointestinal haemorrhage, achieved an uninterrupted 6-year remission without maintenance therapy before the first relapse occurred. Despite maintenance treatment for the remaining 23 patients, precipitous drops in platelet counts commonly occurred following or during a viral infection. At other times a fall in platelet count occurred without any antecedent event. In either situation a short course of prednisolone intensification of 2 to 4 weeks usually returned the platelet count to the previous stable level. Five of the partial responders required the addition of azathioprine of 25 to 75 mg daily to maintain a stable platelet count when the daily prednisolone dose was reduced to 10 mg or less.

Table III – Response to corticosteroid therapy and splenectomy in 32/37 patients with chronic ITP

Treatment Modality and Response*	Sex		Total No. of Patients	Response Rate (%)
	F	M		
Corticosteroid therapy	30	2	32	
Complete response	13	1	14	43.7
Partial response	10	0	10	31.3
Refractory	7	1	8	25.0
Splenectomy	7	1	8	
Complete response	2	0	2	25.0
Partial response	4	1	5	62.5
Refractory	1	0	1	12.5

*Response definitions are as follows:
complete - normal platelet count sustained by daily prednisolone dose <10 mg or rarely, no maintenance therapy;
partial - improved platelet count but below normal range and requires maintenance prednisolone and/or azathioprine therapy;
refractory - no response

Six women from the subgroup of partial responders developed either SLE (4 patients) or Evan's syndrome (2 patients) after 14 to 33 months of clinical monitoring (Table IV). It may be significant that 5 of these women were way above the peak age, third or early fourth decade is the local experience, for autoimmune disorders to develop. They do not appear to share any common histocompatibility antigens between them. In treatment responses they appeared to be a uniform subgroup in that in spite of a suboptimal platelet response to prednisolone prescribed for the ITP, they all demonstrated a rapid normalisation of platelet counts when prednisolone was re-intensified for the secondary autoimmune disorders.

Table IV – Profile of six women who evolved secondary autoimmune disorders 14 to 33 months after the onset of ITP.

	Clinical Profile			Evolved Serological Markers		
Secondary Autoimmune Disorders	Age of onset of ITP (years)	Presenting platelet count x 10^9/l	Latency period to development of Secondary Disorders (months)	DCT positive (with haemolysis)	ANA Positive	Raised anti-DNA level
Evan's Syndrome						
Patient #1	53	30	21	Yes	No	No
#2	58	25	15	Yes	No	No
Systemic Lupus Erythematosus						
Patient #1	46	10	33	No	Yes	Yes
#2	35	40	14	Yes	Yes	Yes
#3	43	20	18	No	Yes	Yes
#4	41	15	26	No	Yes	Yes

DCT - direct Coombs' test
ANA-Antinuclear antibody

Eight patients were refractory to prednisolone therapy. Splenectomy resulted in 2 complete and 5 partial remissions (Table III). The patient who was refractory to splenectomy was able to achieve a partial response when azathioprine was added to her prednisolone treatment after the spleen was removed. No spontaneous remission was recorded for this cohort of 37 patients followed for 4 to 15 years. It is unknown if any of the 5 patients who defaulted after the diagnosis was made remitted spontaneously.

Three patients died 2 to 7 years after the diagnosis of ITP was made. A 47-year-old woman died of massive intracerebral haemorrhage when she relapsed a second time. Her additional risk factor was the 15-year suboptimally controlled diabetes mellitus. The other 2 deaths were due to fulminant gram negative septicaemia in steroid dependent, splenectomised patients. One was a 22-year-old male Indian Singaporean whose blood culture grew *Klebsiella pneumoniae*. The other, a 21-year-old Chinese Burmese woman, succumbed to *Acinetobactor* septicaemia. Both patients had received pneumococcal vaccination with Pneumovacc prior to splenectomy.

DISCUSSION

The long-term tracking of chronic ITP in the West is credited to Wintrobe et al who reported on 52 untreated patients followed for 5 to 29 years[1]. An unusually high incidence of spontaneous recovery was reported in that early study due probably to the authors' inclusion of childhood ITP patients. Later reviews which concentrated on adult patients emphasised the rarity of spontaneous long-term remission[2-4]. The majority of adults with ITP tend to wax and wane in the severity of their symptoms and the degree of thrombocytopenia with the exception of those whose remission is achieved through splenectomy[2,5]. No spontaneous recovery was observed in this cohort of 37 patients. The 5 untreated male patients showed a fluctuation between mild to moderate thrombocytopenia during an average follow up interval of more than 6 years. Although 14 out of 32 treated patients normalised their platelet counts within 6 weeks of commencement of prednisolone treatment, only one patient could be weaned off treatment. She had a 6-year unmaintained remission before she experienced a relapse. This experience contrasts greatly with claims of up to 21% long-term unmaintained remissions in the West[6-8]. All the partial responders and almost all the complete responders in this local cohort of chronic ITP patients required continuous maintenance of 5 to 10 mg prednisolone daily in addition to intermittent, short courses of increased prednisolone dosage during relapses.

The response to splenectomy of 80-85% complete remission (CR) in Western reports[5-8] also contrasts sharply with the 25% CR of this review. This difference may be explained in two ways. The success of splenectomy depends on the removal of the major organ of antibody-coated platelet destruction and anti-platelet antibody production. For some chronic ITP patients, the main site of platelet destruction is not the spleen but the reticuloendothelial system of the liver or bone marrow[8]. Such patients, at best, respond only partially to splenectomy. Using indium-labelled platelet localisation, it is possible to define for a given patient where the predominant site of platelet destruction occurs. As this facility is not available here, it is not possible to document if the high rate of incomplete response to splenectomy in the local patients is attributable to this explanation. Probably the more likely explanation lies in the exclusion of patients who could have responded but who declined splenectomy for various non-medical reasons .Whereas 60-80% of western ITP patients underwent splenectomy eventually,[6,7] only 8 out of 32 symptomatic patients (25%) in this study accepted splenectomy. This reluctance has led to the local practice of exploring various alternate medical options such as the use of non-steroidal immunosuppressive agents, intermittent intravenous administrations of vincristine or human immunoglobulins. In the West the first 2 alternate medical options are strictly reserved for postsplenectomy failures.

The mortality rate of chronic ITP is given as 5-20%, the higher figure being from a report on refractory patients[7,10,11]. Intracranial haemorrhage is the immediate cause of death in most cases[2]. Of the 3 deaths in this review, one was the consequence of thrombocytopenic intracranial haemorrhage. The 2 patients who succumbed to gram negative septicaemia were postsplenectomy patients who had required the continuation of corticosteroid therapy because of incomplete responses to splenectomy. Infection-related deaths in asplenic persons are usually caused by *Streptococcal pneumoniae*[4]. Gram negative septicaemia is not a widely recognised risk in such people. The long-term prednisolone treatment was probably the predisposing factor in these 2 local asplenic patients.

Chronic ITP as an early manifestation of SLE had been reported to occur in 3 to 16% of patients[5,12]. These early authors attributed the high incidence to an unmasking or acceleration of latent SLE by splenectomy. This view is no longer accepted[4]. The similarities of these 2 autoimmune disorders can be seen in the young female preponderance and the high incidence of HLA-DRw2 allo-antigen in both conditions[13,14]. The 4 women who developed SLE and the 2 who evolved into Evan's syndrome 14 to 33 months after the diagnosis of ITP did not share any

similarity in their HLA profile. Clinically, they appeared to form a special subset of ITP, in that they were of an older age group, who responded suboptimally to corticosteroid treatment initially but responded with prompt reversal of their thrombocytopenia when the prednisolone dosage was increased for their secondary autoimmune disorders. A plausible explanation for this apparent change in steroid sensitivity with the advent of the secondary disorders may be one of a relative sparing of antibody-coated platelets by the reticuloendothelial macrophages whose phagocytic function is stretched by having to remove from circulation the immune complexes (in SLE) and autoantibody-coated erythrocytes (in the Evan's syndrome). The unfortunate experience of 2 gram negative septicaemic deaths in asplenic, steroid-dependent patients cautions against the hasty recommendation of splenectomy especially to this subset of patients whose development of secondary autoimmune disorders requiring long-term corticosteroid treatment, puts them into this potentially high risk category.

CONCLUSION

This prospective study of 37 chronic ITP Asian patients bears out the pronounced female predilection recorded in the western communities. All the three racial groups were proportionately represented. The women tend to manifest a more severe degree of thrombocytopenia at diagnosis. Five out of 7 male patients with persistent, mild to moderate thrombocytopenia remain untreated on a follow up of more than 6 years. Spontaneous remission was not observed nor was there any permanent prednisolone-induced complete remission that was unmaintained. The low rate of complete response to splenectomy, 25% as compared to more than 80% in western reports, may simply be a reflection of the inadvertent exclusion of likely responders who decline the operation for nonmedical reasons. An interesting subset of older women inclined towards a secondary autoimmune disorder after the first year, typically responded suboptimally to corticosteroid therapy initially but normalised their platelet counts promptly when the dosage of prednisolone was increased for the treatment of the newly evolved secondary disorders. Only one death in this group of chronic ITP patients was directly related to thrombocytopenic haemorrhage. Two asplenic patients requiring maintenance prednisolone therapy died of gram negative septicaemia. As it is now standard practice to prescribe chronic ITP patients pneumococcal vaccination prior to splenectomy and every 3 years thereafter, the pattern of fatal bacterial infections in the postsplenectomy patients may change to less virulent microorganisms if steroid or non-steroid immunosuppression is continued following splenectomy.

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