

A Study of Idiopathic Thrombocytopenic Purpura (ITP) Patients over a Ten-year Period

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Abstract

Adult idiopathic thrombocytopenic purpura (ITP) is an autoimmune disorder caused by antiplatelet autoantibodies that cause platelet destruction by the reticuloendothelial system. The disease has been well-documented in the West. We studied 78 ITP patients diagnosed and followed up in a tertiary hospital, over a 10-year period, to give a profile of our local patients and their response to treatment. The majority of patients were females and fall in the 20 to 39 years age group. 21.8% were asymptomatic at presentation. The mean presenting platelet count was $31 \times 10^9/L$. Complete response rate to steroid treatment was 46.7%. Thirty-seven patients (47.4%) underwent splenectomy with a success rate of 64.9%. 6.4% required multiple drugs to maintain a stable platelet count. There was no spontaneous, long-term remission in this series. 10.3% of our patients eventually developed an autoimmune disease. ITP has a variable clinical course and treatment has to be highly individualised.

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Introduction

Idiopathic thrombocytopenic purpura (ITP) is an immunoregulatory disorder in which antibodies damage platelets leading to their removal by cells of the reticuloendothelial system (RES).¹ This occurs mainly in the spleen which is also the primary site of synthesis of these antiplatelet antibodies. Patients with chronic ITP have a variable clinical course. ITP is a haematologic disorder for which appropriate diagnostic and treatment strategies are uncertain. Wintrobe et al² reported on 52 untreated patients followed up for 5 to 29 years. This has given us an insight into the disease of chronic ITP in the West. Thirty-seven of our own local patients followed up for 4 to 15 years have been reported by Kueh³ in 1995. In this study we evaluated 78 of our chronic ITP patients diagnosed and followed up in the Department of Haematology, Singapore General Hospital over a 10-year period from 1987 to 1996, to determine their clinical profile and response to different treatment modalities.

Materials and Methods

Chronic ITP is a clinical diagnosis based on the exhaustive exclusion of disorders and situations known to be associated with thrombocytopenia.

Patients included in this study presented to the Department over a 10-year period from 1987 to 1996.

They satisfy the following criteria:

- 1) at least 12 years of age,
- 2) no recent ingestion of drug known to cause thrombocytopenia,
- 3) no recent infection,
- 4) no hepatosplenomegaly or lymphadenopathy,
- 5) confirmed thrombocytopenia (platelets count $<140 \times 10^9/L$),
- 6) no clinical or laboratory evidence of microangiopathy or disseminated intravascular coagulation (DIC),
- 7) no evidence of chronic liver disease with hypersplenism,
- 8) insufficient criteria to diagnose connective tissue disease such as systemic lupus erythematosus (SLE) or rheumatoid arthritis (RA) at presentation, and
- 9) normal or increased numbers of megakaryocytes on bone marrow aspirate or biopsy.

Eighty-five patients were diagnosed to have ITP over a 10-year period from 1987 to 1996. Seven patients defaulted follow-up and were not evaluated.

We examined the 78 remaining patients' presenting history and physical examination. The presenting platelet count and sites of bleeding were documented. Drug history and family history were noted.

All patients had bone marrow aspirates or biopsies showing normal or increased megakaryocytes. Sero-

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logical evidence of autoimmune disease such as anti-nuclear antibody (ANA), anti-double-stranded DNA (Anti-ds DNA), rheumatoid factor were assessed. The response to the various modalities of treatment including steroids, azathioprine, danazol, cyclophosphamide, vinca alkaloids, gammaglobulins, vitamin C, Anti-D immunoglobulin and splenectomy were evaluated.

We also examined the complications of the disease or treatment. Of particular interest was the profile of patients who eventually developed an autoimmune disease.

Results

Eighty-five patients were diagnosed to have ITP in the Department of Haematology, Singapore General Hospital, from 1987 to 1996. Seven patients defaulted follow-up. The remaining 78 patients were evaluated.

Clinical Profile

The clinical profile of the 78 patients is summarised in Table I. Of the 78 patients, 57 were females (73.1%) and 21 were males (26.9%). The majority were in the 20 to 39 years age group. There was no significant ethnic predilection.

Duration of Follow-up

All the 78 patients were on regular follow-up for a period of 1 month to more than 9 years at the time of evaluation. The median follow-up duration was 5.5 years.

Initial Clinical Presentation

Patients with ITP can be asymptomatic at presentation despite their thrombocytopenia or manifest different severity of bleeding secondary to their low platelet count. Their initial clinical presentation is summarised in Table II.

(A) Asymptomatic

Seventeen (21.8%) of our patients were asymptomatic at presentation. They were detected on routine medical examination and referred to our Department for further evaluation. These patients had platelet counts ranging from $3 \times 10^9/L$ to $62 \times 10^9/L$. The mean platelet count for these asymptomatic patients was $29 \times 10^9/L$.

(B) Symptomatic

Minor or moderate bleeding

- (i) Petechiae, gum bleeding or epistaxis—45 of our patients (57.7%) had petechiae, gum bleeding or epistaxis on presentation. Their platelet count ranged from $1 \times 10^9/L$ to $81 \times 10^9/L$. The mean platelet count was $30 \times 10^9/L$.
- (ii) Menorrhagia—9 patients (11.5%) with menorrhagia had their platelet counts ranging from $10 \times 10^9/L$ to $60 \times 10^9/L$. The mean platelet count was $42 \times 10^9/L$.
- (iii) Haematuria—2 patients (2.6%) presented with haematuria. Their platelet counts were $3 \times 10^9/L$ and $6 \times 10^9/L$.

TABLE I: CLINICAL PROFILE OF 78 IDIOPATHIC THROMBOCYTOPENIC PURPURA PATIENTS

Patient characteristics	No. of patients	%
(I) Sex		
Male	21	26.9
Female	57	73.1
(II) Age (y)		
10 to 19	17	21.8
20 to 29	17	21.8
30 to 39	18	23.1
40 to 49	6	7.7
≥50	20	25.6
(III) Race		
Chinese	61	78.2
Malay	8	10.3
Indian	8	10.3
Others	1	1.3

TABLE II: INITIAL CLINICAL PRESENTATION OF 78 IDIOPATHIC THROMBOCYTOPENIC PURPURA PATIENTS

Symptoms	No. (%)	Platelet count range ($\times 10^9/L$)	Mean platelet count ($\times 10^9/L$)
Asymptomatic	17 (21.8)	3 to 62	29
Minor/moderate bleeding			
Petechiae, gum bleeding or epistaxis	45 (57.7)	1 to 81	30
Menorrhagia	9 (11.5)	10 to 60	42
Haematuria	2 (2.6)	3 to 6	4.5
Major bleeding			
Intracranial haemorrhage	1 (1.3)	5	-
Gastrointestinal haemorrhage	4 (5.1)	4 to 45	16

Major bleeding

- (i) Intracranial haemorrhage—1 patient (1.3%) with a platelet count of $5 \times 10^9/L$ presented with a subdural haematoma. This 60-year-old man had an evacuation of the haematoma and subsequently required a combination of prednisolone, azathioprine and danazol for control of his ITP.
- (ii) Gastrointestinal haemorrhage—4 patients (5.1%) presented with melena. Their platelet count ranged from $4 \times 10^9/L$ to $45 \times 10^9/L$. There was no local cause found on gastroscopy in all these patients.

The mean platelet count on presentation for all patients was $31 \times 10^9/L$ and the median platelet count was $35 \times 10^9/L$.

Treatment

(A) Not treated

Only 1 patient (1.3%) with a platelet count of $60 \times 10^9/L$ was not treated.

(B) Steroids alone

Thirty patients (38.5%) were treated with steroids alone. Prednisolone was initiated at a daily dose of 1 mg/kg body weight. A* complete response was seen in 14 patients (46.7%). A** partial response was seen in 16 patients (53.3%). None of the patients was*** refractory.

Steroid complications: 6 patients had cushingnoid features
1 patient became hypertensive
2 patients had infections

Relapse off steroids: 8 patients (27%) relapsed when the steroid dose was tailed down and eventually taken off. They relapsed 1 to 10 months after the steroids were stopped.

Response definitions:

* Complete response—normal platelet count sustained by daily prednisolone <10 mg or no maintenance therapy

** Partial response—improved platelet count but below normal range and requiring maintenance prednisolone and/or azathioprine

*** Refractory—no response

(C) Steroids and Splenectomy

Thirty-seven patients (47.4%) had splenectomies for steroid-dependence and/or steroid complications. Splenectomies were performed from as early as 1 month to 7 years after the diagnosis of ITP. Twenty-four patients (64.9%) were in complete remission after splenectomy. The other 13 patients required combination therapy to maintain a stable platelet count. One patient developed femoral arterial thrombosis postoperatively (platelet count $800 \times 10^9/L$) and required a bypass.

(D) Steroids and Azathioprine

Five patients (6.4%) were on prednisolone and azathioprine. All had refused splenectomy. Two had complete responses (40%) and 3 (60%) were partial responders.

(E) Combination Therapy

Five patients (6.4%) were each on multiple drugs to maintain a stable platelet count. They had all refused a splenectomy. The modalities include azathioprine, danazol, cyclophosphamide, vinca alkaloids, anti-D immunoglobulin, cyclosporine, gammaglobulin, vitamin C and immunoadsorption. The responses in these patients were, at best, partial.

Death from Haemorrhage

None of our patients died as a result of haemorrhage.

Development of Secondary Autoimmune Diseases

Eight patients (10.3%) who were partial responders eventually developed systemic lupus erythematosus

(SLE) (4 patients), Evan's syndrome (3 patients) and rheumatoid arthritis (RA) (1 patient) after a period of 1 month to 3 years after the diagnosis of ITP. Their profile is illustrated in Table III.

Discussion

Adult ITP is an autoimmune disorder caused by one or more antiplatelet autoantibodies usually directed to the platelet glycoprotein IIb/IIIa complex, GPIb/IX complex or both that cause platelet destruction by the reticuloendothelial system. Chronic ITP is a diagnosis of exclusion, with also the exclusion of other types of immune thrombocytopenia.

In western communities, ITP is most common in young women.² This is also reflected in our series with the majority (73.1%) of the patients being female. The majority of the patients were in the 20 to 39 years age group (30.8%). The youngest patient was a 12-year-old boy who presented with a platelet count of $28 \times 10^9/L$ and was asymptomatic. The three oldest patients presented at the age of 67 years, with platelet count ranging from 33 to $71 \times 10^9/L$. The symptoms were minor (petechiae) in 2 and 1 was asymptomatic. However, all these three patients were partial responders requiring combination therapy to maintain a stable platelet count. In our series, 21.8% of our patients were asymptomatic and have a mean platelet count of $29 \times 10^9/L$ —this is lower than the generally documented level of $50 \times 10^9/L$.² It is also found that patients with counts less than $10 \times 10^9/L$ run the risks of gastrointestinal, genitourinary and central nervous system bleeding.^{4,5} This is consistent with the findings in our patients with haematuria (platelet count of $3 \times 10^9/L$, $6 \times 10^9/L$), intracranial haemorrhage ($5 \times 10^9/L$) and 3 of the 4 patients with gastrointestinal haemorrhage ($4 \times 10^9/L$, $6 \times 10^9/L$, $8 \times 10^9/L$). The 60-year-old patient who suffered a subdural haematoma was well after evacuation and required prednisolone, azathioprine and danazol for maintenance.

Idiopathic thrombocytopenic purpura is a heterogeneous disease and has been treated with agents that vary in efficacy, toxicity and cost. In 1994, the American Society of Hematology established an expert panel to review published data on the effectiveness of diagnostic tests and treatments for ITP and developed evidence-based practice guidelines for the diagnosis and treatment of ITP.⁵ It is a general practice not to treat patients with platelet count of $\geq 30 \times 10^9/L$.^{4,5} However in our series of 78 patients, only 1 patient with a platelet count of $60 \times 10^9/L$ was not treated. The mean platelet count was $31 \times 10^9/L$. This implies that a significant number of patients would be "over-treated" by such guidelines. In our 30 patients treated with steroids alone, the complete response rate was 46.7%. This is comparable to a local study done by Kueh³ (43.7%). We had a higher partial response rate (53.3%) compared to 31.3% in the other

TABLE III: PROFILE OF 8 PATIENTS WHO DEVELOPED SECONDARY AUTOIMMUNE DISEASES

AI disease	Sex	Age of onset of ITP(y)	Platelet count on diagnosis (x 10 ⁹ /L)	Latency period from ITP diagnosis to AI disease	Serological results
SLE					
Patient A	F	40	45	3 years	ANA+ ≥1/640 AntidsDNA+
Patient B	F	20	2	3 years	ANA+ ≥1/640 AntidsDNA+
Patient C	F	21	10	1 month	ANA+ ≥1/640 AntidsDNA+
Patient D	F	20	25	1 year	ANA+ AntidsDNA+
Evan's Syndrome					
Patient 1	F	29	22	3 months	ANA/dsDNA negative
Patient 2	M	33	16	1 year	ANA/dsDNA negative DCT +
Patient 3	M	52	6	1 month	ANA/dsDNA negative DCT +
Rheumatoid Arthritis					
Patient	F	57	3	6 months	ANA/dsDNA negative Rh factor negative

AI: autoimmune; SLE: systemic lupus erythematosus

local series. This could be due to the fact that we had no refractory responders compared to 25% in Kueh's series. The relapse rate on steroids was 27% in our series. The response to splenectomy of 64.9% complete remission (CR) in our series is higher compared to 25% in Kueh's series. This could be due to more patients who were agreeable for splenectomy. Western reports show a CR of 80% to 85%.⁶⁻⁹ They also have a higher percentage of ITP patients who underwent splenectomy (60% to 80%),^{7,8} compared to our series (47.4%) and Kueh's series (25%). Perhaps this is related to our Asian culture of avoiding any operations if possible in one's lifetime.

We feel that the treatment of ITP has to be highly individualised. Despite practice guidelines being laid down for the treatment of ITP,⁵ much of the treatment options is determined by the physician's "feel of need" to increase a particular patient's platelet count, the patient's willingness to accept a certain drug and its side-effects or splenectomy and the patient's concomitant diseases, especially those that predispose to easier haemorrhage at a lower platelet count. From our clinical experience, the patient's willingness to accept a splenectomy is a major factor in the management of the disease. This may be related to our culture in which exists a belief that any operation with removal of an organ is undesirable. This, together with cosmetic concerns and fear of infections post-splenectomy may lead a patient to select a drug option over splenectomy. Multiple drugs are

available, with different side-effects. Patients have also been known to prematurely discontinue a drug should they find the side-effects unacceptable. Hence, in the course of the treatment of ITP, very much of the treatment options is determined by the physician, the patient's preferences and his pre-existing disease conditions.

Reviews on chronic ITP have emphasised the rarity of spontaneous, long-term remission.¹⁰⁻¹² The majority of adults with ITP tend to wax and wane in the severity of their symptoms and degree of thrombocytopenia. There was no spontaneous remission in this cohort of 78 patients followed up for a period of 1 month to more than 9 years. In the West, long-term unmaintained remission rates are around 21%.⁶⁻⁸ In our cohort, there was only 1 patient who is in unmaintained complete remission after an 8-month follow-up. In another local series,³ there was also no spontaneous remission in a cohort of 37 patients. All the partial responders and almost all the complete responders in our series required continuous maintenance of 5 to 10 mg prednisolone in addition to other drugs. Five patients (6.4%) required more than 2 modalities to maintain a stable platelet count. The differences in treatment response rates and remission rates between the different studies, both local and in the West, are likely to be due to multiple factors. Chronic ITP is a heterogeneous disease in itself and its management being influenced by multiple factors including the physician's threshold to initiating treatment, physician and

patient's choice of agent used and different subjective definition of response to a mode of therapy before changing or adding another agent are all factors which will eventually influence the response and remission rates.

The mortality rate of chronic ITP is usually given as 5% to 20%,^{8,13,14} with the patients succumbing to infections and thrombocytopenic haemorrhage. In our series, there was no mortality from similar causes. This could be due to the small number of patients in our series. The patient cohort, type and severity of infections, antibiotics usage and the severity and treatment of haemorrhage are all determinants of mortality which are difficult to compare in the different studies. There was no documented case of infection-related deaths in our asplenic steroid-dependent patients. All our splenectomised patients received pneumococcal vaccination prophylaxis.

One patient developed femoral arterial thrombosis secondary to post-splenectomy thrombocytosis. His platelet count was $800 \times 10^9/L$ and a bypass was performed. He was stable subsequently.

Chronic ITP as an early manifestation of SLE has been reported to occur in 3% to 16% of patients.^{9,15} In our cohort, 4 patients (5.1%) developed SLE after a period of 1 month to 3 years upon diagnosis of ITP. All these patients were female and 3 of them were in their twenties. This is consistent with both autoimmune disorders being associated with a young female preponderance and a high incidence of HLA-DRw2 allo-antigen.¹⁵⁻¹⁷ The thrombocytopenia improved with higher steroid doses used for control of their secondary autoimmune disorders. Three patients (3.8%) developed Evan's syndrome 1 month to 1 year after diagnosis of ITP. Two were male patients and 1 female. Interestingly, all underwent splenectomy but achieved only partial response requiring steroids and various other drugs for control of disease. One patient (1.3%) developed RA after 6 months. She required only steroids for control of RA and stabilisation of platelet count. Hence, we feel that there is a need to regularly monitor for features of autoimmune disease in the follow-up of our ITP patients.

In conclusion, our study of our local patients has given us an insight of the disease profile in our local patients and highlighted the various areas in which it may be different from ITP in the western communities.

Conclusion

This study of 78 ITP patients diagnosed over a 10-year period, with follow-up period ranging from 1 month to more than 9 years, in a tertiary hospital, gives a profile of these patients and their response to treatment. There was a female predilection as seen in the western communities. The majority of the patients were in the 20 to 39 years age group. 21.8% of the patients were asymptomatic at presentation. The majority of patients had minor bleeding on presentation with major bleeding

occurring in 5 patients. The mean platelet count on presentation was $31 \times 10^9/L$. Complete response rate to steroid treatment was 46.7%, comparable to the rate observed in another local study. The complete remission rate for splenectomy was 64.9%, a rate lower than the 80% to 85% seen in western communities. All other patients required combination therapy with various drugs to maintain a stable platelet count. There was no mortality secondary to haemorrhage or infection in this series. There was also no spontaneous, long-term remission in these 78 patients. Eight (10.3%) patients developed secondary autoimmune diseases including SLE, Evan's syndrome and RA. We feel that certain aspects of the disease profile are different in our local patients compared to the western communities and despite general guidelines being available the treatment of ITP has still to be highly individualised.

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