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Clinical outcome and treatment pattern linked with chronic immune thrombocytopenia at a tertiary care teaching hospital

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Abstract
ITP is considered as 'isolated thrombocytopenia with no clinically apparent associated conditions or other causes of thrombocytopenia' by the American Society for Haematology guidelines. So it is thus a condition that, to a large extent, is a diagnosis of exclusion. Asymptomatic patients of chronic ITP do not require treatment as per the guidelines unless they are bleeding or the platelet count in adults is <30,000/cmm. So here our aim is to retrospectively analyze our data regarding the factors responsible for initiating therapy and the type of therapy instituted based upon the affordability of patients and severity of bleed. We performed an observational study in our Institute in patients diagnosed as chronic ITP from the years Oct 2016 Sept 2019. Out of 113 patients diagnosed as ITP, 17 patients had chronic ITP. Patients with persistent and chronic ITP had a platelet count ranging between 5000/cmm to <1,00,000/cmm. Most common site of bleeding was cutaneous bleed in the form of petechial spots and ecchymosis (15 out of 17 patients). The majority of the patients had steroids as first treatment along with rituximab while second treatment was diverse. Children with asymptomatic thrombocytopenia did not receive any therapy. None of our patients underwent splenectomy. Identification of common clinical presentation and their treatment strategy in our study can helps to that patients who are at increased risk of this disease.

Keywords: Chronic ITP, rituximab, thrombocytopenia, ecchymosis

Introduction
Immune thrombocytopenia, has become a diagnosis of exclusion. Bone marrow examination is not necessary to diagnose ITP irrespective of age in patients presenting with typical ITP. The American Society of Hematology (ASH) has laid down guidelines for the diagnosis and management of patients with ITP in 1996 and 2011 [1, 2]. ASH 1996 guidelines mentioned ITP as, Idiopathic Thrombocytopenia which was changed to Immune thrombocytopenia in 2011 guidelines and the duration of thrombocytopenia in Chronic ITP was changed from 6 months (1996) guidelines to >12 months in ASH 2011 guidelines. Similarly, 1996 ASH emphasized that ITP was the result of increased destruction of platelets while the 2011 added the fact that there was both due to decreased production as well as increased destruction of platelets. The incidence of primary ITP in adults is 3.3/100 000 adults per year with a prevalence of 9.5 per 100 000 adults.

A clinical syndrome of bleeding and purpura consistent with a diagnosis of immune thrombocytopenia (ITP) was described by Welsh of long before platelets were identified as the cellular component of blood playing an essential role in primary haemostasis [3]. In the American Society for Haematology guidelines ITP is defined as 'isolated thrombocytopenia with no clinically apparent associated conditions or other causes of thrombocytopenia [4]. It is thus a condition that, to a large extent, is a diagnosis of exclusion. Clinical observation and experience indicate a spectrum of manifestations ranging from trivial bruising to catastrophic haemorrhage. The incidence of fatal haemorrhage is as high as 10.4% according to some studies [5]. The literature suggests that older patients appear to have more severe bleeding manifestations [6]. It has been reported that 43% of patients achieve a remission with a platelet count of > 100 X 109/l, thus implying that the majority of patients have a continuous or relapsing chronic disease state. So here in this study, our aim is to analyze the clinical manifestations of ITP and the type of therapy and its effect instituted based upon the affordability of patients and severity of bleed.

Materials and Methods

The study was done on a prospective basis in a tertiary care teaching hospital. An institutional ethics committee approval was obtained prior to the study. An institutional ethics committee approval was obtained prior to the study. All patients aged ranged from 0 to 70 years with a diagnosis of ITP were included in the study.

Study population

Clinical data of 113 patients diagnosed as ITP from October 2016 till September 2019 were analysed retrospectively. Clinical data were retrospectively collected from medical charts for each patient and completed by telephone interviews with patients and physicians by using a standardized questionnaire.

Result

Out of 113 patients diagnosed as ITP, 17 (14%) patients were classified as persistent and chronic ITP. A thorough history was taken and physical examination done to look for sites of bleeding, lymph node enlargement, hepato-splenomegaly and any growth failure features. Laboratory investigations included- Complete blood count, peripheral blood film examination, HIV, HCV, HBV testing.

Table 1: Age grouping of chronic ITP patient.

Age	0-10 yrs	10-20 yrs	20-30 yrs	30-40 yrs	40-50 yrs	50-60 yrs	60-70 yrs
No. of patients	1	4	4	2	1	3	2

Male: female ratio in pediatric population (age ≤18 yrs) was 3:2 & Male: female ratio in adults (age > 18 yrs) was 3:1. (Table. 1)

While evaluating for secondary causes of ITP, four out of 16 patients had Anti-Nuclear Antibody titre positive with underlying Systemic Lupus Erythematosis (SLE) or Rheumatoid Arthritis (RA), while the rest 12 patients were screened negative for the test**.**

Platelet count

Patients with persistent and chronic ITP had a platelet count ranging between 5000/cmm to <1,00,000/cmm. However, we have taken into consideration the platelet count at which patients had either spontaneous bleeding or was <30,000/cmm in adults requiring therapy as per the guidelines (Table. 2)

Table 2: Platelet count details

Platelet count	<5000/ cmm	5000-10,000/cmm	11,000-20,000	21,000-30,000/cmm
No. of patients	7	2	6	2

Table 3: Site of bleed data

Site of bleed	Intracranial Hemorrhage	Wet purpurea	Gum bleed	epistaxis	hematemesis	melena	hematuria	Skin bleed	menorrhagia
No. of Patients	2	9	10	6	2	7	1	15	7

Most common site of bleeding was cutaneous bleed in the form of petechial spots and ecchymosis (15 out of 17 patients) (Table. 3). This was followed by the gum bleeding seen in 9 patients and presence of mucosal bleed in 10 patients. The patients with buccal mucosal bleed or wet purpura had a count of <5000/cmm. Six patients had epistaxis, of which four were >50 years age and had hypertension as a comorbidity. The rest two were less than 25 yrs age and had no precipitating underlying condition. Hematemesis was seen in two patients both presenting at >50 years age. Seven patients had Upper GI bleeding and had melena. None required any interventional procedure and bleeding was managed conservatively with injectable Proton Pump Inhibitors (PPIs) and platelet transfusions along with initiation of therapy for ITP. Only a single 37 year male presented with Hematuria and KUB bladder showed a small stone which was managed conservatively. Majority of the females (7 out of 12) presented with menorrhagia as a bleeding manifestation and had proportionate anemia. Among the females, one had not attained menarche while 3 were post menopausal.

Table 4: Therapy of the identified ITP patients

Agents used	Steroids only	Steroids + Dapsone + Azathioprine	Rituximab + Steroids	Rituximab + Steroids + CsA	Eltrombopag	Eltrombopag + Steroids
Number of patients	Nil	3	5	6	4	2

None of the 17 patients received steroids as a single agent, as they had already received it as first line therapy when they were newly diagnosed as well as during subsequent relapses. Steroids were combined with second line agents like Rituximab, Eltrombopag or Dapsone and Azathioprine with an intention to prevent relapses and maintain a response (Table. 4).

Patients who were unable to afford Rituximab or Eltrombopag, were treated with Dapsone and azathioprine in combination with steroids, after assessing the G6PD activity. Three out of eighteen (16%) patients received a combination of prednisolone 1 mg/kg/day, Dapsone 100 mg OD and Azathioprine 1-2 mg/kg/day.

Response to Therapy

Response were defined as mentioned in the IMWG criteria. The mean and median time to clinical cessation of bleeding, irrespective of the regimen used was 5 days.

Table. 5: Reponses details to therapy.

No of patient	Therapy received	Time to Clinical Resonse	Time to Hematological Response to Therapy	Response achieved		Duration of therapy	Duration of Response	Relapse
				Complete remission	Remission			
1.	Rituximab+ Dexa+CsA	3 days	15 days	Yes		1 month	27 months	No
2.	Rituximab+ Dexa+CsA	2 days	5 days	Yes		1 month	38 months	No
3.	Rituximab+ Dexa+CsA	3	8	Yes		1 month	22 months	No
4.	Rituximab+ Dexa+CsA	11	21	yes		1	14	yes
5.	Rituximab+ Dexa+CsA	5	10		yes	1	8	yes
6.	Rituximab+ Dexa+CsA	10	28		yes	1	6	yes
7.	Steroids +Rituximab	2	21	yes		1	9.5	yes
8.	Steroids +Rituximab	2	5	yes		1	11	yes
9.	Steroids +Rituximab	5	12	yes		1	8	yes
10.	Steroids +Rituximab	7	10	yes		1	19	no
11.	Steroids +Rituximab	5	15	yes		1	36	yes
12.	Dapsone+Steroids +Azathioprine	2	28		yes	24	24	yes
13.	Dapsone+Steroids +Azathioprine	6	21		yes	18	18	yes
14.	Dapsone+Steroids +Azathioprine	7	32		yes	16	21	yes
15.	Steroids+Revolade	7	14	yes		6	24	no
16.	Steroids+Revolade	3	15	yes		1	4	no

Of the 17 patients analysed, one patient, a 13 year old boy had a platelet count of >30,000/cmm and never had any bleeding manifestations apart from skin bleeds and hence did not require any treatment for ITP. He was diagnosed as a case of ALPS after the flow cytometer as mentioned in earlier paragraph. The patient is on 3 monthly follow up.

Two patients receiving Steroids and Rituximab and another two receiving Dapsone, steroids and Azathioprin received Revolade on relapse and are presently in remission (Table. 5).

Discussion

Immune thrombocytopenia (ITP) is defined as a platelet count <100 x 10^9/L while excluding other causes of thrombocytopenia. It is further differentiated into primary ITP or secondary ITP based upon the underlying cause, as many of the treatments of secondary ITP target the underlyimg disorder. Primary ITP has been divided into newly diagnosed (<3 months from diagnosis), persistent (3-12 months from diagnosis), or chronic (>12 months since diagnosis) by the International Working Group on ITP in 2009. Asymptomatic patients of chronic ITP do not require treatment as per the guidelines unless they are bleeding or the platelet count in adults is <30,000/cmm.

Idiopathic thrombocytopenic purpura is a relatively uncommon problem. The demographics, clinical presentation and the response to treatment can be very varied. Most studies have shown a female preponderance for ITP. Godeau *et al*. [7] showed a male: female ratio of 1:1.9 in a cohort of 122 patients. Johanna *et al*. [8] showed a male: female ratio of 1:1.7 in a study which had 152 patients. Our study had a male: female ratio of 3:1 and 3:2 in adult and pediatric population respectively. There is female predilection in our study. There is a predilection for female patients in younger adults, but the prevalence of ITP in men and women is fairly even in the elderly (65 years) [9].

All the patients had undergone a bone marrow aspiration and biopsy procedure before categorizing them in the chronic ITP group to rule out the possibility of amegakaryocytic thrombocytopenia or any other underlying bone marrow pathology. Though the current guidelines suggest that a bone marow examination is not necessary irrespective of age in patients presenting with typical ITP [2].

In therapy, high dose Dexamethasone, 40 mg OD x 4 days, with 375 mg/m^2 rituximab weekly for 4 weeks was administered to five patients (27%) [10]. Triple therapy regimen was offered to six patients (27%) who had severe bleeding manifestations and severe thrombocytopenia but were unable to afford full dose rituximab regimen. The triple therapy (TT4) included oral Dexamethasone 40 mg for days 1 to 4, oral cyclosporine 2.5- 3 mg/kg daily for day 1 to 28 and intravenous low dose rituximab 100 mg for days 7, 14, 21 and 28 as mentioned by Choi *et al*. [11]. The therapy was well tolerated with no serious adverse side effects. Eltrombopag, as a single agent was initiated at a dose of 50 mg OD in four patients, of which two patients had a loss of response (platelet count <30 x 10^9/L) to steroids, Dapsone and Azathioprine combination and two had a loss of response to Steroids and Rituximab combination therapy. Two patients, were initiated on Prednisolone @ 1 mg/kg and Eltrombopag with an intention to rapidly taper steroids once a response was achieved. Dosage of eltrombopag was adjusted as mentioned in the product monograph of Revolade [12].

Conclusion

Identification of common clinical presentation and their relationship to platelet count helps identify patients who are at increased risk. The treatment pattern will enable the researcher to find the most suitable strategy and probable information for a effective treatment of the ITP patients.

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