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Primary Immune Thrombocytopenia in Malaysia: A Review

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ABSTRACT

Primary immune thrombocytopenia is an autoimmune condition in which the quantity of platelets in the blood is significantly decreased. It can affect both pediatrics and adults. Immune thrombocytopenia is linked to recurrent bruising and bleeding due to low platelet levels, which can be caused by a variety of reasons, including impaired thrombopoiesis and immunological responses that contribute to platelet destruction under pathological conditions. The disease has been considered one of the identified hematological diseases in Malaysia. A total of six primary immune thrombocytopenia articles among children and adults in Malaysia were identified in the academic database published between 2008 and 2020. The publication on primary immune thrombocytopenia in Malaysia was considered low, with a rate of 0.50 publications per year. Even though immune thrombocytopenia is recognizable in the country, the disease is not gaining much attention compared to other hematological and autoimmune disorders. The true incidence of primary immune thrombocytopenia in the country could not be determined, and thus remains unknown. Patient outcomes and disease clinical presentation are case-specific, pointing to immune thrombocytopenia rather than a collection of clinical conditions with similar symptoms. Loss of immunological tolerance to platelet antigens and primary hemostasis failure are two of the most common symptoms. Because of the heterogeneity of the patient population and their characteristics, clinicians have to choose an appropriate therapeutic regimen.

1. INTRODUCTION

Immune thrombocytopenia (ITP) is an acquired disease defined by a reduction in platelet count induced by

platelet autoantibodies, as well as an increased risk of bleeding symptoms [17], [23]. The terms, definitions and clinical criteria that have been used in ITP studies somehow are inconsistent and unreliable in the management of this hematological disorder. In response to heterogeneity and discrepant criteria, [22] suggested avoiding the terms "idiopathic" and "purpura", and instead using "primary" to indicate the absence of secondary or underlying causes.

Primary ITP (pITP) is defined by the International Working Group (IWG) as an autoimmune disorder characterized by isolated thrombocytopenia (platelet count $<100 \times 10^9$/L) in the absence of other causes and disorders that may be linked with thrombocytopenia. Though no clinical or laboratory criteria are available to accurately diagnose pITP, it is diagnosed by exclusion [11]. The exact process by which the human immune system turns against itself (autoimmunity) and causes ITP is unclear. There are presently no valid clinical or laboratory criteria for determining an appropriate diagnosis [22]. Although bleeding symptoms are not always evident, the major clinical concern in patients with pITP is an increased risk of bleeding [11].

In Malaysia, ITP has been recognized as one of the hematological diseases along with coagulation disorders, hemoglobinopathies and hematological malignancies. A Clinical Practice Guideline (CPG) on the Management of Immune Thrombocytopenic Purpura has been released by the Ministry of Health (MOH) and the Academy of Medicine of Malaysia [17]. The CPG was established using worldwide recommendations and the most recent medical research to help local practitioners make well-informed decisions about the diagnosis and treatment of ITP.

2. Primary Immune Thrombocytopenia Reported in Malaysia

The incidence of pITP in the country is less known. In the past a decade, only six pITP were published between 2008 and 2020 with only 0.5 publications per year (based on our research utilising Web of Science, SCOPUS and ScienceDirect as search engine) (Table 1). Immune thrombocytopenia is not gaining much attention compared to other hematology and autoimmune disease such as systemic lupus erythematosus [10], [14], [28], rheumatoid arthritis [28], [1], [13] and thalassemia [8], [4], [26].

Our country's health institutions maintain a data repository for both pITP and secondary ITP (sITP). However, those data have not been shared and published, leaving the exact incidence and prevalence of ITP in Malaysia unclear. It was reported low incidence of ITP patients in Singapore which was 78 patients over a 10-years period and overall admission rate for ITP patients in Thailand were 7.68 per 100,000 populations [27], [30].

Table 1: List of pITP publications in Malaysia in 2008 to 2020.

	Author	Title
1	[16]	Audit of pediatric hematology-oncology outpatients in Kuala Lumpur
2	[9]	Chronic adult primary immune thrombocytopenia (ITP) in the Asia-Pacific region
3	[29]	Spontaneous bilateral peripapillary, subhyaloid and vitreous hemorrhage with only minor platelet deficit in idiopathic thrombocytopenic purpura
4	[18]	Spontaneous intracranial hemorrhage in children with chronic immune thrombocytopenic purpura
5	[24]	Idiopathic thrombocytopenic purpura and total knee arthroplasty: how low can you go

6	[3]	Laparoscopic splenic artery ligation in a patient with immune thrombocytopenia with intracranial hemorrhage

3. Review on clinical manifestation of pITP

The mean (SD) age of patients at diagnosis was 28.86 (20.22) years. Meanwhile, the mean initial platelet count was 30.29 X 10^9/L. At the time of diagnosis, patients were presented with menorrhagia, gum bleeding, ecchymosis or petechiae [18], [29].

Those signs and symptoms were the most prevalent clinical aspects of ITP, and they ranged from asymptomatic patients with mild bruising to frank bleeding in any body part [17]. There are three types of immune tolerance defects in ITP: 1) peripheral tolerance problems that occur when the immune system is stimulated, 2) differentiation blocks with skewed peripheral B-cell subsets, and 3) central tolerance abnormalities emerging during development or in the bone marrow. The clinical features of specific instances of ITP may be explained by the underlying processes linked to each of them. Platelet-specific ITP is thought to be caused by a lack of peripheral tolerance and is less likely to recur after treatment as compared to central tolerance defects that impact many cell types and are more prone to relapse owing to intrinsic autoreactivity [6].

[28] reported that a patient with a moderate anemia hemoglobin count of 93 g/L developed spontaneous bilateral peripapillary, subhyaloid and vitreous hemorrhage [29]. Ophthalmic involvement is exceptionally rare. Even severe thrombocytopenia with a platelet count of <50,000 is rarely sufficient to cause significant retinal hemorrhage. However, thrombocytopenia with anemia is a known risk factor, and retinal hemorrhages associated with ITP have only been described when severe anemia is present [6]. There are a few case reports in literature that describe comparable retinal hemorrhages linked to ITP [15], [20]. Both studies reported that the hemorrhages were associated with severe anemia and considered secondary to ITP. Severe anemia has been closely associated with retinopathy and thrombocytopenia [2].

Intracranial hemorrhage (ICH) is rare but devastating complication of ITP especially in children and aggressive treatment may be appropriate. Severe hemorrhage may lead to mortality or neurologic sequelae [19]. Four patients with persistent ITP developed ICH [18]. The time between the beginning of ITP and the onset of ICH ranged from 1 to 8 years. At the time of their cerebral bleed, all the patients were profoundly thrombocytopenic, with a platelet count of <10 x 10^9/L. All the patients survived, with three of them having complete neurological recovery and one having a minimal neurological deficit. [3], reported a 44 -year-old man with three-year history of ITP, who defaulted follow-up and treatment, presented with acute on chronic subdural hemorrhage. He did not respond to intravenous immunoglobulin (IVIg) and high dose oral prednisolone. Laparoscopic splenic artery ligation was done and twelve hours post splenic artery ligation, his platelet counts increased to 115 and 240x10^9/L the following day. Left Burr-hole surgery and external ventricular drainage were performed subsequently.

It has been reported that ICH is commonly associated with ITP that occurs in both genders of pediatrics and adults [18], [3], [5], [7], [21], [25]. According to a report from the International Cooperative Study, ICH complications affect adults more than pediatrics, with 10 of 1784 children and 6 of 340 adults with newly diagnosed ITP experiencing it [12]. The hemorrhage may be acute or chronic and occur within the meninges, which are epidural, subdural and subarachnoid bleeds [18], [3], [5], [7].

This review subjected to several limitations. The previous pITP literature was from the case reports and no

single publication was on retrospective or prospective studies. Several pITP literature were not provided much information [9], [16], described a prospective study focusing on the range and type of cancers among pediatric hematology-oncology outpatients. After eliminating the malignancies and secondary hematological disorders, 43 pediatric patients were diagnosed with pITP with no further information [16]. [9], addressed the chronic adult pITP in the Asia-Pacific region [9]. Their work was in conjunction with and responded to the international report emphasizing on ITP [22]. Thus, [9], gathered 22 hematologists representing the Asia-Pacific to describe the unique ITP landscape in the region in terms of general diagnostic practices, common secondary causes to ITP and initial treatments [9].

4. Conclusions

The publication of pITP in Malaysia is low, and the true incidence of the autoimmune disease remains unknown. The disease is not rare in the country but did not receive much attention compared to other autoimmune diseases and hematological disorders. Future research should focus on a large-scale retrospective study from the local health institutions to get a clearer picture of the incidence and diagnosis of pITP in Malaysia.

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