Isolated Thrombocytopenia in Thai Children: Etiology and Result of Bone Marrow Aspiration Study

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ABSTRACT

Background: Isolated thrombocytopenia (IT) refers to an entity of low platelet count without abnormalities of other lineages. Previous studies revealed that the main cause of IT in children without atypical features i.e. hepatosplenomegaly or adenopathy was immune thrombocytopenia (ITP), while acute leukemia and aplastic anemia (AA) were other possible causes. However, there was no previous study in Thailand to identify the cause of IT.
Objective: To study the bone marrow aspiration (BMA) result in Thai children with IT and to identify the cause of IT in Thai children.
Methods: This was a retrospective chart review of children younger than 15 years old with IT who were diagnosed at Siriraj Hospital during January 1996 to December 2010. All patients had BMA to identify the cause of thrombocytopenia. Demographic data, clinical manifestation, laboratory results including BMA finding, diagnosis and initial treatment were collected and analyzed.
Results: One hundred and twenty-nine patients were enrolled to the study. All patients had normal or increased megakaryocytes in their bone marrow, and none of them had more than 5% of blast cells. Most patients (97.7%) were diagnosed as acute ITP while 2.3% were diagnosed with neonatal alloimmune thrombocytopenia. None of the patients had acute leukemia or AA.
Conclusion: The BMA result of most patients in this study was compatible to that of ITP, that is none of the patients had acute leukemia or AA. The most common cause of IT in Thai children is acute ITP. This result suggested that BMA in children with IT before starting treatment is not necessary.

Keywords: Bone marrow aspiration, children, isolated thrombocytopenia, ITP, Thailand

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INTRODUCTION

Isolated thrombocytopenia refers to an entity of low platelet count without the abnormalities of other lineages. Generally, the level of platelet count below 150,000/mm^3 is a cut point for the definition of thrombocytopenia.[1] However, a platelet count lower than 100,000/mm^3 has more clinical significance and has been established as the threshold for diagnosis of thrombocytopenia in a newer guideline.[2] In children who are otherwise well and no atypical features such as hepatosplenomegaly, adenopathy, skin, skeletal and cardiac abnormalities, then immune thrombocytopenia (ITP) is the main cause of isolated thrombocytopenia.[3,4] In some circumstances, thrombocytopenia with explainable cause of anemia are still considered as a typical presentation of ITP.[3] In addition, other conditions such as

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acute leukemia, aplastic anemia (AA), congenital thrombocytopenia, autoimmune disease and immunodeficiency syndrome can also present with isolated thrombocytopenia.[4-7]

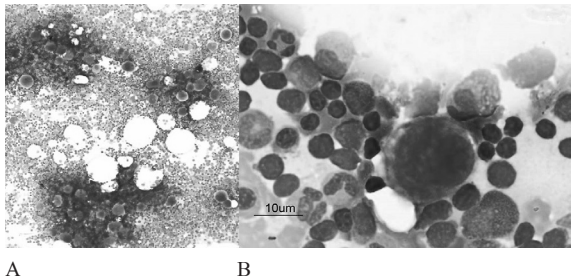
The treatment of ITP varies in each institute and consists of corticosteroids, IVIG or observation.[3,8-10] It is known that corticosteroids are also one of the main medications for acute leukemia, although giving corticosteroids alone prior to definite chemotherapy can have negative impact on a patient's survival.[11] Therefore, it is important to exclude acute leukemia before starting treatment of ITP, especially in those who require corticosteroids treatment.

Since there is no specific test for ITP, the diagnosis of ITP relies on the exclusion of other possible causes of isolated thrombocytopenia. Bone marrow aspiration (BMA) has been used widely to differentiate acute leukemia from ITP. The BMA result in ITP patients shows normal or increased megakaryocytes, while other series are unremarkable (Fig 1).[3,12] In contrast, leukemia patients have a significant increase in number of blast cells in bone marrow.

In Thailand, there has been no previous study to define the cause of isolated thrombocytopenia in children. Therefore, we plan to conduct a study to determine the etiology of isolated thrombocytopenia in Thai children for a better understanding and proper management of such patients.

MATERIALS AND METHODS

We performed a retrospective chart review of children younger than 15 years old with isolated thrombocytopenia who were diagnosed at Siriraj Hospital between January 1996 and December 2010. The main objective of our study was to study the BMA result of these children and to identify the cause of isolated thrombocytopenia in an otherwise well child.



A B

Fig 1. Bone marrow smear (Wright stain) in acute ITP patients shows A) increase number of megakaryocyte B) young form megakaryocyte.

The inclusion criteria was patients with platelet count less than 100,000/mm^3 without neutropenia, no blast cell in peripheral blood smear, and no atypical features (i.e. hepatosplenomegaly, adenopathy, and abnormalities of skin, skeletal or cardiac system). Patients with identifiable causes of anemia were also included in the study. The exclusion criteria were patients with unexplained anemia, recurrent thrombocytopenia, or with known systemic diseases that had thrombocytopenia as one of their manifestations such as congenital thrombocytopenia, autoimmune disease and immunodeficiency syndrome.

According to our institutional policy, all children with isolated thrombocytopenia need bone marrow aspiration (BMA) to exclude other possible causes before starting treatment. Therefore, we enrolled the patients in this study by identifying them from the BMA records and medical records in the database of the Division of Hematology/Oncology, Department of Pediatrics, Faculty of Medicine Siriraj Hospital. First of all, patients who had platelet count less than 100,000/mm^3 with normal absolute neutrophil count (ANC) for age,[13] no blast cell in peripheral blood smear, and no atypical features were identified. Secondly we checked for the possible causes of anemia in those who had low hemoglobin. Patients with identifiable cause of anemia were included in the study; whereas, those with unexplained anemia were excluded.

The patient's demographic data, clinical manifestations, laboratory results including complete blood count (CBC) and BMA findings, patient's diagnosis, initial treatment, and the final diagnosis at 1-year visit were collected and analyzed using SPSS version 16.0.

This study was approved by the Ethic Committee of Faculty of Medicine Siriraj Hospital (COA number Si.389/2014).

RESULTS

One hundred and twenty-nine patients were enrolled to the study, including 16 patients (12.4%) who had low hemoglobin level for age according to the World Health Organization criteria[14], but with identifiable causes of anemia. The etiologies of anemia in these patients were blood loss (4.6%), iron deficiency anemia (3.9%), thalassemia disease (2.3%), physiologic anemia (0.8%) and anemia of prematurity (0.8%).

Demographic data

The majority of the patients were presented before 6 years of age. Forty-six patients (35.7%) had preceding viral infection, and 20 patients (15.5%) recently received vaccination within 1 month prior to the onset of thrombocytopenia (Table 1). Of note, some patients might receive multiple doses of vaccine in each visit. Most patients presented with skin bleeding, and had petechiae or ecchymosis on examination (Table 2).

Complete blood count

About half of the patients had platelet count lower than 10,000/mm^3, with a mean platelet count of 13,110/mm^3 and median platelet count of 8,000/mm^3. All patients had normal platelet morphology with mean platelet volume of 9.3 fL. The WBC series was unremarkable. The mean hemoglobin level was 11.4 g/dl and the mean hematocrit was 34.2% (Table 3).

BMA result

The majority of the patients (93.8%) had increased megakaryocytes, and 38.8% had increased amount of young megakaryocytes. Megakaryocyte morphology was normal in all

TABLE 1. Demographic data of patients with isolated thrombocytopenia (n =129)

Parameter		Number of patients (%)
Age group:	0-1 month	7 (5.4)
	1 month-1 year	32 (24.8)
	1-6 years	58 (45)
	6-12 years	29 (22.5)
	12-15 years	3 (2.3)
Median Age at diagnosis		3 years (range 2 days -14 years)
Gender:	Female	54 (41.9)
	Male	75 (58.1)
Underlying disease		
Thalassemia		3 (2.3)
G-6-PD deficiency anemia		1 (0.8)
History of viral infection		
Upper respiratory tract infection		44 (34.1)
Hand, foot and mouth disease		1 (0.8)
Varicella infection		1 (0.8)
Median time to the onset of thrombocytopenia		7 days (range 1-31 days)
Recent Immunization		
HBV		14 (11)
DTP/OPV		9 (7)
BCG		4 (3.1)
Hib		4 (3.1)
MMR		3 (2.3)
JE		1 (0.8)
Median time to the onset of thrombocytopenia		14 days (range 1-30 days)

G-6-PD: Glucose-6-Phosphate dehydrogenase, HBV: Hepatitis B vaccine, DTP: Diphtheria, Tetanus, Pertussis vaccine, OPV: Oral polio vaccine, Hib: Hemophilus influenzae type B vaccine, MMR: Mumps, measles, rubella vaccine, JE: Japanese encephalitis vaccine

TABLE 2. Clinical presentations and physical examination of patients with isolated thrombocytopenia (n =129)

Parameter	Number of patients (%)
Clinical presentation	
Skin bleeding	126 (97.7)
Mucosal bleeding	27 (20.9)
Upper GI hemorrhage	3 (2.3)
Hypermenorrhea	1 (0.8)
Epistaxis	12 (9.3)
Hematuria	2 (1.6)
Physical examination	
Petechiae	107 (82.9)
Ecchymosis	78 (60.5)
Wet purpura	28 (21.7)
Bleeding per gum	9 (7)
Subconjunctival hemorrhage	5 (3.9)

TABLE 3. Result of the complete blood count in patients with thrombocytopenia

Parameter	All patients (n = 129)	Patients without anemia (n = 113)	Patients with anemia (n = 16)
Hemoglobin (g/dl)			
Mean ± SD	11.4 ± 1.6	11.8 ± 1.2	8.5 ± 1.2
Median (range)	11.5 (5.4-17.7)	11.7 (10-17.7)	8.8 (5.4-9.9)
Hematocrit (%)			
Mean ± SD	34.2 ± 4.7	35.4 ± 3.6	25.9 ± 3.8
Median (range)	34.3 (17.4-53.4)	34.8 (30-53.4)	27.1 (17.4-31.6)
White blood cell (/mm^3)			
Mean ± SD	11, 350.7 + 3,911.5	11,364 + 3,968.5	11,255 + 3,607.7
Median (range)	10,600 (3,200-22,400)	10,600 (3,200-22,400)	11,215 (5,000-16,500)
Median percentage (%)			
N (range)	39.3 (15-86)	40.5 (15-86)	32.8 (16.9-76)
L (range)	46.5 (9-86)	46 (9-86)	53.5 (15-76)
Eo (range)	0.7 (0-29)	0.7 (0-29)	0.8 (0-10.9)
Mo (range)	5.2 (0-14)	5 (0-14)	6.9 (10-12)
Median count (/mm^3)			
ANC (range)	3,603 (1,049-17,920)	3,711 (1,049-17,920)	3,359 (1,100-10,621)
ALC (range)	4,289 (793-16,259)	4289 (793-16,259)	4,255 (2,360-9,862)
Platelet count (/mm^3)			
Mean ± SD	13,110 ± 15,258	13,408.9 ± 15,633	11,000 ± 12,506
Median (range)	8,000 (1,000-85,000)	8,000 (1,000-85,000)	6,500 (1,000-53,000)
Range of platelet count (/mm^3)			
<10,000	70* (54.3%)	61* (54%)	9* (56.2%)
10,001-20,000	36* (27.9%)	30* (26.5%)	6* (37.5%)
20,001-50,000	16* (12.4%)	16* (14.2%)	0* (0%)
>50,000	7* (5.4%)	6* (5.3%)	1* (6.3%)
MPV (fL)	9.3 (8.3-14.2)	9.3 (8.3-14.2)	N/A

* Number of patients, N: Neutrophil, L: Lymphocyte, Eo: Eosinophil, Mo: Monocyte, ANC: Absolute neutrophil count, ALC: Absolute lymphocyte count, MPV: Mean platelet volume, N/A: non-applicable

patients. Forty percent of the patients had increased lymphocyte count, especially in those who were younger than 6 years old. Blast cell was reported in 71.3% of the patients, although none of them had blast cells more than 5%. The bone marrow cellularity, erythroid series, myeloid series and histiocytic series were shown in table 4. There was no difference in the BMA result of the patients with and without anemia.

Diagnosis

After reviewing the patients' history, physical examination, CBC and BMA result, 126 patients (97.7%) were diagnosed as acute ITP, and 3 patients (2.3%) were diagnosed as neonatal alloimmune thrombocytopenia (NAIT). None of them had acute leukemia or AA. The diagnosis of NAIT was confirmed by human platelet antigen (HPA) typing. The BMA result of acute ITP and

TABLE 4. Result of the bone marrow aspiration study

Parameter	Number of patients (%)		
	All patients (n=129)	ITP (n=126)	NAIT (n=3)
Cellularity			
Normocellularity	111 (86)	109 (86.5)	2 (66.7)
Hypocellularity	8 (6.2)	8 (6.4)	0 (0)
Hypercellularity	10 (7.8)	9 (7.1)	1 (33.3)
Megakaryocyte number			
Normal	8 (6.2)	6 (4.8)	2 (66.7)
Increase	121 (93.8)	120 (95.2)	1 (33.3)
Megakaryocyte maturation			
Normal	79 (61.2)	78 (61.9)	1 (33.3)
Increase young form	50 (38.8)	48 (38.1)	2 (66.7)
Megakaryocyte morphology			
Normal	129 (100)	126 (100)	3 (100)
Abnormal	0 (0)	0 (0)	0 (0)
Erythroid series			
Normal	109 (84.5)	108 (85.7)	1 (33.3)
Increase	20 (15.5)	18 (14.3)	2 (66.7)
Myeloid series			
Normal	117 (90.7)	115 (91.3)	2 (66.7)
Abnormal; increase eosinophil	12 (9.3)	11 (8.7)	1 (33.3)
Lymphocyte			
Normal	77 (59.7)	76 (60.3)	1 (33.3)
Increase	52 (40.3)	50 (39.7)	2 (66.7)
Histiocyte			
Normal	127 (98.4)	125 (99.2)	2 (66.7)
Increase	2 (1.6)	1 (0.8)	1 (33.3)
Hemophagocytic activity			
Normal	129 (10%)	126 (100)	3 (100)
Increase	0 (0%)	0 (0)	0 (0)
Blast cell			
No blast cell	37 (28.7)	35 (27.8)	2 (66.7)
< 5%	92 (71.3)	91 (72.2)	1 (33.3)
5-30%	0 (0%)	0 (0)	0 (0)

ITP: Immune thrombocytopenic purpura, NAIT: Neonatal alloimmune thrombocytopenia

NAIT patients were shown in table 4. All NAIT patients were diagnosed before 1 month old, while 4 of the ITP patients (3.1%) presented before 1 month of age.

Treatment and clinical course

Most patients received corticosteroids as the treatment of choice (Table 5). At the end of the 1-year follow-up, 86.8% of patients had platelet recovery while 13.2% remained thrombocytopenic and were diagnosed as chronic ITP. There was no difference in the BMA result of patients with acute and chronic ITP. (Data has not been shown)

DISCUSSION

Isolated thrombocytopenia is an important problem in children. From previous reports, ITP was the most common etiology of this condition in an otherwise well child, which was followed by leukemia and AA, but to a much lesser extent.[3-5] Since the treatment of these conditions is different and some treatments might compromise the outcome of other conditions,[11] identifying the cause of isolated thrombocytopenia is very important.

Of all the 129 patients from our study, the majority of them were preschool children younger than 6 years old which was the common age group of acute ITP.[3] Preceding viral infection was found in only 35.7% of our patients, compared with more than 60% in other reports of ITP.[3,15] The reason for the lower incidence of viral infection in our study is unclear, although it is possible that some patients might have only mild symptoms, so the parents were unaware of the viral infection. Twenty patients (15.5%) in this study had recent vaccination before the onset of thrombocytopenia. It is known that mumps, measles and rubella (MMR) vaccine is responsible for most cases of vaccine related thrombocytopenia.[16,17] Interestingly, data from our study showed that patients who received viral hepatitis B vaccination had the highest incidence of thrombocytopenia, followed by diphtheria-tetanus-pertussis and oral polio vaccines. However, the correlation between these vaccines and isolated thrombocytopenia cannot be confirmed and might be a co-incidence, because the patients who received these vaccines were among the common age group for ITP.

TABLE 5. Initial treatment of patient with acute ITP (n =126)

Treatment	Number of patient (%)
Observation	2 (1.6)
Corticosteroids	107 (84.9)
IVIG	13 (10.3)
Corticosteroids and IVIG	4 (3.2)

The initial platelet count was lower than 20,000/mm^3 in 82.2% of the patients and lower than 10,000/mm^3 in more than half of them, but there was only minor skin bleeding in the majority of patients. This can be explained by the fact that most platelets in the peripheral circulation of ITP patients are young and have normal or enhanced function.[18] However, the severity of bleeding might be increased if the platelet counts are very low.

The BMA result showed that 71.3% of the patients had blast cells in their bone marrow, but none of them met the criteria for diagnosis of leukemia which required blast cells more than 25% and 20% in acute lymphoblastic leukemia and acute non lymphoblastic leukemia respectively. Although the percentage of blast cell was below 5% in all patients, the presence of blast cells in the majority of patients raised some concerns. Since none of them developed leukemia after a 1-year follow-up, the blast cells that were found in the bone marrow might be just bone marrow hematogones which have similar morphology to the leukemic blast cell and can only be distinguished by using a special investigation such as 4-color flow cytometry.[19]

All patients in our study had normal to increased megakaryocytes with increased young megakaryocytes in some of them, which is a typical BMA finding in ITP patients.[3,12] However, this finding is not specific to ITP, but can be found in all thrombocytopenia caused by peripheral destruction of platelets.

After reviewing the history, physical examination, laboratory result and BMA result carefully, most of the patients in our study were diagnosed as acute ITP and none of them had leukemia. Only 3 patients had diagnoses other

than ITP; all of them had the result of the HPA typing different from their mothers and were diagnosed as NAIT. The BMA result in all 3 patients revealed normal or increased megakaryocytes, similar to that of ITP patients, because thrombocytopenia in NAIT was also caused by the destruction of platelets in peripheral circulation.[20] There was also higher proportion of the young megakaryocytes, erythroid series and lymphocytes in the bone marrow of NAIT patients. However, since the number of NAIT patients in this study was quite small when compared to the ITP group, these findings might not have significance and need further observation. The only difference between ITP and NAIT patients in our study was the age at presentation and the positive result of HPA typing. All NAIT patients were younger than 1 month, while only 4 of the ITP patients (3.1%) were diagnosed before 1 month of age. However, this is not beyond expectations since NAIT usually presents within a few days after birth.[21]

Historically, BMA was recommended in most cases of isolated thrombocytopenia especially when corticosteroids treatment was considered. Nevertheless, the need for BMA was questioned since several reports revealed that BMA was not required in patients who do not have atypical features of ITP.[4,9,12,22] However, the role of BMA before starting corticosteroids has been controversial. A recent guideline from the American Society of Hematology suggested that BMA before corticosteroids treatment is not necessary, although there was a lower degree of confidence and no strong evidence to support (level 2C).[7]

In Thailand, the need for BMA in a patient with isolated thrombocytopenia is still a debatable issue, especially in the institute that uses corticosteroids as a first line treatment, since there is a concern that corticosteroids might delay the diagnosis and compromise the outcome of leukemia. However, the result of our study showed that the cause of isolated thrombocytopenia without atypical features in most patients is ITP and none of them had leukemia. This finding confirms the result of previous reports that the major etiology of isolated thrombocytopenia in an otherwise well child was ITP.[3-5] Hence, in our opinion, the need for BMA in such patients is not necessary. Nevertheless, those who present with atypical features such as hepatosplenomegaly, adenopathy, and skin, skeletal or cardiac abnormalities should have BMA to evaluate for other possible etiologies.[3,7]

The presence of anemia in thrombocytopenic patients might be a clue to other conditions such as acute leukemia and AA. Therefore, most experts have suggested performing BMA to exclude such conditions. In our study, 16 patients (12.4%) were found to have anemia, but with explainable causes in all of them. Thus, we decided to include them to the study. Our study showed that there was no difference in the BMA result of those with and without anemia, and all of them were diagnosed as acute ITP. Thus, we also suggest that BMA might not be necessary in this group of patients if the cause of anemia can be identified.

CONCLUSION

The BMA result of most patients in this study was compatible to that of ITP; none of the patients had acute leukemia or AA. Acute ITP is the most common cause of isolated thrombocytopenia in Thai children who are otherwise well. This result suggests that BMA before starting treatment is not necessary in such children, regardless of the steroid treatment.

REFERENCES

1. Cheng CK, Chan J, Cembrowski GS, van Assendelft OW. Complete blood count reference interval diagrams derived from NHANES III: stratification by age, sex, and race. Lab Hematol 2004;10:42-53.
2. Rodeghiero F, Stasi R, Gernsheimer T, Michel M, Provan D, Arnold DM, et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. Blood 2009;113:2386-93.
3. Blanchette VS, Carcao M. Childhood acute immune thrombocytopenic purpura: 20 years later. Semin Thromb Hemost 2003;29:605-17.

4. Calpin C, Dick P, Poon A, Feldman W. Is bone marrow aspiration needed in acute childhood idiopathic thrombocytopenic purpura to rule out leukemia? Arch Pediatr Adolesc Med 1998;152:345-7.
5. McIntosh N. Is bone marrow investigation required in isolated childhood thrombocytopenia? Lancet 1982;1:956.
6. Kottayam R, Rozenberg G, Brighton T, Cohn RJ. Isolated thrombocytopenia in children: thinking beyond idiopathic thrombocytopenic purpura and leukaemia. J Paediatr Child Health 2007;43:848-50.
7. Neunert C, Lim W, Crowther M, Cohen A, Solberg L, Jr., Crowther MA. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. Blood 2011;117:4190-207.
8. Arnold DM, Kelton JG. Current options for the treatment of idiopathic thrombocytopenic purpura. Semin Hematol 2007;44:S12-23.
9. George JN, Woolf SH, Raskob GE, Wasser JS, Aledort LM, Ballem PJ, et al. Idiopathic thrombocytopenic purpura: a practice guideline developed by explicit methods for the American Society of Hematology. Blood 1996;88:3-40.
10. Eden OB, Lilleyman JS. Guidelines for management of idiopathic thrombocytopenic purpura. The British Paediatric Haematology Group. Arch Dis Child 1992;67:1056-8.
11. Revesz T, Kardos G, Kajtar P, Schuler D. The adverse effect of prolonged prednisolone pretreatment in children with acute lymphoblastic leukemia. Cancer 1985;55: 1637-40.
12. Halperin DS, Doyle JJ. Is bone marrow examination justified in idiopathic thrombocytopenic purpura? Am J Dis Child 1988;142:508-11.
13. Boxer LA. How to approach neutropenia. Hematology Am Soc Hematol Educ Program 2012;2012:174-82.
14. McLean E, Cogswell M, Egli I, Wojdyla D, de Benoist B. Worldwide prevalence of anaemia, WHO Vitamin and Mineral Nutrition Information System, 1993-2005. Public Health Nutr 2009;12:444-54.
15. Kuhne T, Buchanan GR, Zimmerman S, Michaels LA, Kohan R, Berchtold W, et al. A prospective comparative study of 2540 infants and children with newly diagnosed idiopathic thrombocytopenic purpura (ITP) from the Intercontinental Childhood ITP Study Group. J Pediatr 2003;143:605-8.
16. France EK, Glanz J, Xu S, Hambidge S, Yamasaki K, Black SB, et al. Risk of immune thrombocytopenic purpura after measles-mumps-rubella immunization in children. Pediatrics 2008;121:e687-92.
17. Bertuola F, Morando C, Menniti-Ippolito F, Da Cas R, Capuano A, Perilongo G, et al. Association between drug and vaccine use and acute immune thrombocytopenia in childhood: a case-control study in Italy. Drug Saf 2010;33: 65-72.
18. Rand ML, Dean JA. Platelet function in autoimmune (idiopathic) thrombocytopenic purpura. Acta Paediatr Suppl 1998;424:57-60.
19. McKenna RW, Washington LT, Aquino DB, Picker LJ, Kroft SH. Immunophenotypic analysis of hematogones (B-lymphocyte precursors) in 662 consecutive bone marrow specimens by 4-color flow cytometry. Blood 2001; 98:2498-507.
20. Arnold DM, Smith JW, Kelton JG. Diagnosis and management of neonatal alloimmune thrombocytopenia. Transfus Med Rev 2008;22:255-67.
21. Bussel JB, Primiani A. Fetal and neonatal alloimmune thrombocytopenia: progress and ongoing debates. Blood Rev 2008;22:33-52.
22. Geddis AE, Balduini CL. Diagnosis of immune thrombocytopenic purpura in children. Curr Opin Hematol 2007; 14:520-5.