Ochsner Journal 17:115–117, 2017

Immune Thrombocytopenia and Obesity: Predictive Relationship

Ehab Hanafy, MD, Mohammed Al Pakra, MD

Prince Sultan Oncology Center, King Salman Armed Forces Hospital, Tabuk, Kingdom of Saudi Arabia

Background: Chronic refractory immune thrombocytopenia (ITP) is defined as the failure of any modality to maintain the platelet count above $20 \times 10^3/\mu L$ for an appreciable time without unacceptable toxicity. To date, certain predictive factors have been associated with refractory ITP. However, none of the published studies has declared the possible association between obesity and refractory ITP.

Case Reports: We present the cases of 3 children with ITP who failed to achieve remission on different therapeutic approaches including rituximab, vincristine, and romiplostim. The 3 children had obesity as a common feature.

Conclusion: We present these cases to propose a possible association between obesity and refractoriness of ITP to different therapeutic approaches and to emphasize the need for further study to establish whether a causal relationship exists.

Keywords: *Pediatric obesity, purpura–thrombocytopenic–idiopathic*

Address correspondence to Ehab Hanafy, MD, Prince Sultan Oncology Center, King Salman Armed Forces Hospital, 71411 Tabuk, Kingdom of Saudi Arabia. Tel: +966-50-329-8454. Email: ehab.hmahmoud@gmail.com

INTRODUCTION

Immune thrombocytopenia (ITP) is defined as isolated thrombocytopenia with normal bone marrow and the absence of other causes of thrombocytopenia. ITP is an immune-mediated disorder characterized by accelerated and premature destruction of platelets by the reticuloendothelial system.[1] Chronic refractory ITP is defined as the failure of any modality to maintain the platelet count above $20 \times 10^3/\mu L$ for an appreciable time without unacceptable toxicity. Chronic refractory ITP is uncommon. A review of 6 case series suggested that <10% of adult patients initially diagnosed with ITP may eventually be considered to have refractory disease and require further treatment following failure of splenectomy.[2]

To date, certain predictive factors such as age, sex distribution, history of recurrent bleeding episodes, an insidious disease onset, and the failure of an initial therapeutic response are associated with the refractoriness of ITP.[3] However, none of the published studies has declared the possible association between obesity and refractory ITP. We report the cases of 3 children with refractory ITP, all of whom were obese.

CASE REPORT 1

A 10-year-old male presented with a history of bloody urine and purple dots on the skin following minor trauma of 1-month duration. He had a history of meatal stenosis that was being treated conservatively, but he had no history of hypertension, hyperinsulinemia, dyslipidemia, type 2 diabetes, or asthma. The patient had no other symptoms or signs of bleeding. Family history and psychosocial history were irrelevant.

On examination, the child was hemodynamically stable; looked well; and was active, oriented, and cooperative. His weight was 58 kg, height was 141 cm, and body mass index (BMI) was 27.2 kg/m^2. He looked slightly pale and had wet purpura, diffuse petechiae on the trunk and abdomen, and bruises on both extremities, but he had no organomegaly. Remaining systems review was unremarkable. His platelet count was $10 \times 10^3/\mu L$ (Table 1).

The child was diagnosed with acute ITP, and he was started on steroids with no response. Bone marrow aspirate was consistent with peripheral platelet destruction. A trial of intravenous immunoglobulin (IVIG) resulted in a significant increase in the platelet count ($179 \times 10^3/\mu L$) 48 hours postinfusion. However, the increase was transient; the patient's platelet count fluctuated with time and ranged from $30 \times 10^3/\mu L$ to $90 \times 10^3/\mu L$. Six months later, the patient's platelet count dropped significantly, decreasing to $8 \times 10^3/\mu L$. The decision was made to start rituximab 375 mg/m^2 weekly for 4 weeks. During the month of treatment, the patient's platelet count minimally increased to $43 \times 10^3/\mu L$, but it dropped again below $20 \times 10^3/\mu L$ after discontinuation of rituximab. The parents refused a splenectomy, and the child was lost to follow-up.

CASE REPORT 2

A 12-year-old female presented with nosebleed and purple dots on her arms of 1-week duration. She had no history of gum bleed, bloody urine or stools, preceding

Table 1. Laboratory Results for Patient 1

Laboratory Test	Value
White blood cells	7.6 $\times$ $10^3/\mu L$
Hemoglobin	11.9 g/dL
Platelets	10 $\times$ $10^3/\mu L$
Prothrombin time	12 seconds
Partial thromboplastin time	30 seconds
Blood smear	Normal
Antinuclear antibody	Negative

trauma, hypertension, hyperinsulinemia, dyslipidemia, type 2 diabetes, or asthma. Family history and psychosocial history were irrelevant.

On examination, she looked well and was alert, cooperative, overweight, and pink. Her temperature was 36.6°C, blood pressure was 123/52 mmHg, weight was 56 kg, height was 141 cm, and BMI was 28.1 kg/m^2. Ear, nose, and throat were clear; cardiovascular examination revealed normal heart sounds with no murmur or added sounds; chest showed good bilateral air entry; and the abdomen was lax and soft with no organomegaly. The patient had a few petechiae on the extensor aspects of both arms. Her platelet count was 3 $\times$ $10^3/\mu L$ (Table 2).

The child was diagnosed with acute ITP and received 2 trials of IVIG with minimal response. Bone marrow aspirate was consistent with peripheral platelet destruction. She received a trial of intravenous (IV) methylprednisolone 30 mg/kg/d for 3 days, developed high blood sugar levels, and was diagnosed as having transient steroid-induced hyperglycemia that corrected after discontinuation of methylprednisolone. Second-line therapy of vincristine 1.5 mg/m^2 weekly (total dose of 2 mg) was begun, and she had a significant increase in her platelet count. The regimen of administration was subsequently tailored to once every 2 weeks, then every 3 weeks, and then monthly. The patient's platelet count was maintained within normal limits for almost 1 year. However, after discontinuation of vincristine, her platelet count dropped again, decreasing to $<$20 $\times$ $10^3/\mu L$. At this point, the decision to perform a splenectomy was made as the last chance for cure.

CASE REPORT 3

A 10-year-old male presented with petechial rash on the chest wall and both upper limbs. He had a history of fever and upper respiratory tract infection 1 week before presentation. The patient had no history of gum bleed, bloody urine or stools, or preceding trauma. He had no history of other medical problems. Family history and psychosocial history were irrelevant.

On examination, the patient was well but hypoactive, alert, cooperative, and overweight. His weight was 54 kg, height was 140 cm, and BMI was 27.5 kg/m^2. Ear, nose, and throat were clear; he had normal heart sounds with no murmur or added sounds; chest showed good bilateral air entry; and the abdomen was lax and soft with no organomegaly. The patient had a few petechiae on the chest wall and both arms. His platelet count was 6 $\times$ $10^3/\mu L$ (Table 3).

The child was diagnosed with acute ITP and received a trial of IVIG with no response. Bone marrow aspirate was

Table 2. Laboratory Results for Patient 2

Laboratory Test	Value
White blood cells	6.5 $\times$$10^3/\mu L$
Hemoglobin	13.4 g/dL
Platelets	3 $\times$ $10^3/\mu L$
Prothrombin time	12 seconds
Partial thromboplastin time	36 seconds
Antinuclear antibody	Negative
Thyroid-stimulating hormone	1.23 μU/mL
Free thyroxine (free T4)	12.99 pmol/L
Random blood sugar	6.1 mmol/L

consistent with peripheral platelet destruction. A trial of IV methylprednisolone resulted in a transient elevation of the platelet count. During a period of 1 year, the child presented frequently with low platelet counts and bleeding signs. Every time, he was offered oral prednisone and had a transient response. He was started on subcutaneous romiplostim (Nplate) on a weekly basis. He responded transiently immediately after the dose; however, his platelet count declined again before the next injection despite maximum increments of the medication dosage. The romiplostim was discontinued after failure to achieve a steady platelet count. The patient's parents refused splenectomy, so the patient was kept under regular follow-up. His platelet count never exceeded 20 $\times$ $10^3/\mu L$.

DISCUSSION

To establish a diagnosis of chronic refractory ITP, 2 criteria should be fulfilled. First, the patient should have failed splenectomy and have a continuous requirement for therapies to increase and sustain the platelet count. Second, the patient should either exhibit severe ITP or have a risk of bleeding that in the opinion of the attending physician requires therapy.[4,5]

ITP follows a benign course in most children but has the potential to be life threatening. The risk of primary intracranial bleeding and soft tissue and mucosal bleeding secondary to trauma can cause morbidity and mortality. The lack of evidence-based management protocols is a potential cause for poor management of ITP because no evidence clearly demonstrates that treatment alters the final outcome in any way.[6]

Treatment of ITP can be divided into medical and surgical management. Medical management is further divided into first-line and second-line pharmacotherapy. Medical options for front-line drug therapy are corticosteroids, IVIG, and IV Rh anti-D. Second-line pharmacotherapy principally comprises immunosuppressants and rituximab. These drugs are used when first-line drugs have failed or patients have become intolerant. Immunosuppressants primarily act at the level of T cells.[7]

Certain risk factors are associated with chronic refractory ITP, including a female-to-male ratio of 2.6:1. Approximately 72% of patients $>$10 years are female.[8] Mazigh et al reported that factors predicting development of chronic disease are history of recurrent bleeding episodes, an insidious disease onset, and the failure of an initial

Table 3. Laboratory Results for Patient 3

Laboratory Test	Value
White blood cells	8 $\times 10^3/\mu L$
Hemoglobin	11.2 g/dL
Platelets	6 $\times 10^3/\mu L$
Prothrombin time	14 seconds
Partial thromboplastin time	39 seconds
Antinuclear antibody	Negative
Thyroid-stimulating hormone	1.4 μU/mL
Free thyroxine (free T4)	14.6 pmol/L
Random blood sugar	6.8 mmol/L

therapeutic response.[3] Zeller et al reported that the strongest predictor of chronic disease is insidious onset of symptoms.[9]

Our first and third cases lacked the known risk factors associated with refractory ITP; both patients were males, and their ages did not exceed 10 years. The patient in our second case, however, may have carried a possible risk for refractoriness because of her age and sex. However, none of the 3 patients had insidious onset of the disease, which is the strongest known predictor of chronic disease,[9] and none had a hemorrhagic background. The 3 patients shared the common feature of obesity.

To our knowledge, no cases of chronic refractory ITP in association with overweight and/or obesity have been reported; the only association that has been reported is the morbid obesity that is a consequence of corticosteroid therapy in ITP. However, we propose that obesity may be a new possible risk factor for ITP refractoriness.

The BMI value for children and adolescents (aged 2-19 years) is plotted on Centers for Disease Control and Prevention (CDC) growth charts to determine the corresponding BMI-for-age percentile. Overweight is defined as a BMI at or above the 85th percentile and lower than the 95th percentile, whereas obesity is defined as a BMI at or above the 95th percentile for children of the same age and sex. These definitions are based on the CDC growth charts for the United States and the recommendations of the Expert Committee.[10] A child's weight status is determined based on an age- and sex-specific percentile for BMI rather than by the BMI categories used for adults because the body composition of children varies as they age and varies between boys and girls.[10]

CONCLUSION

We reported the cases of 3 children with ITP who had simple obesity as a common feature and failed to achieve remission after various therapeutic approaches. We propose that obesity could be considered a possible new risk factor when investigating the causes of refractoriness in ITP patients. We emphasize the rarity of reporting the possible association between obesity and ITP refractoriness and recommend more studies that may establish a predictive relationship between obesity and the refractoriness of ITP.

ACKNOWLEDGMENTS

The authors have no financial or proprietary interest in the subject matter of this article.

REFERENCES

1. Latifzadeh SZ, Entezari V. Chronic refractory idiopathic thrombocytopenic purpura (ITP) and Anti-CD20 monoclonal antibody: a case report. *Clin Appl Thromb Hemost*. 2006 Oct; 12(4):489-492.
2. George JN. Management of patients with refractory immune thrombocytopenic purpura. *J Thromb Haemost*. 2006 Aug;4(8): 1664-1672.
3. Mazigh Mrad S, Ouedemi M, Bouyahia O, Gharsallah L, Boukthir S, Gharbi AS. Thrombocytopenic idiopathic purpura: predictive factors for chronic disease [in French]. *Tunis Med*. 2009 Jan; 87(1):72-75.
4. Rodeghiero F, Stasi R, Gernsheimer T, 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 Mar;113(11): 2386-2393. doi: 10.1182/blood-2008-07-162503.
5. Psaila B, Bussel JB. Refractory immune thrombocytopenic purpura: current strategies for investigation and management. *Br J Haematol*. 2008 Oct;143(1):16-26. doi: 10.1111/j.1365-2141. 2008.07275.x.
6. Cines DB, Bussel JB, McMillan RB, Zehnder JL. Congenital and acquired thrombocytopenia. Hematology Am Soc Hematol Educ Program. 2004:390-406. Erratum in: Hematology Am Soc Hematol Educ Program. 2005:543.
7. Warrier R, Chauhan A. Management of immune thrombocytopenic purpura: an update. *Ochsner J*. 2012 Fall; 12(3): 221-227.
8. Beutler E, Lichtman MA, Coller BS, Kipps TJ. *Williams Hematology*. 5th ed. New York, NY: McGraw-Hill; 1995.
9. Zeller B, Rajantie J, Hedlund-Treutiger I, et al. Childhood idiopathic thrombocytopenic purpura in the Nordic countries: epidemiology and predictors of chronic disease. *Acta Paediatr*. 2005 Feb;94(2):178-184.
10. Barlow SE; Expert Committee. Expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: summary report. *Pediatrics*. 2007 Dec;120 Suppl 4:S164-S192.

This article meets the Accreditation Council for Graduate Medical Education and the American Board of Medical Specialties Maintenance of Certification competencies for Patient Care and Medical Knowledge.