Immune Thrombocytopenia as the Initial Manifestation of Pediatric Systemic Lupus Erythematosus: Case Reports

Harapan Parlindungan Ringoringo*

Department of Child Health, Faculty of Medicine, Lambung Mangkurat University, RSD Idaman Banjarbaru, Banjarbaru, Indonesia

Abstract

BACKGROUND: Immune thrombocytopenia (ITP) can precede the onset of systemic lupus erythematosus (SLE) by months to years.

CASE PRESENTATION: A 12-year-old girl weighing 46 kg came to the hospital with the complaint of 12 days-massive menstruation bleeding. The patient is weak, pale. Eyes, ENT, heart, lungs, abdomen: within normal limits, no petechiae. Laboratorium: Hb 8.2 g/dL, leukocytes 7800/uL, platelets 6000/uL, hematocrit 25.1%, segments 71%, lymphocytes 24%, monocytes 4%. Red blood cell (RBC) 1.59 million/uL, mean corpuscular volume (MCV) 94.3fL, mean corpuscular hemoglobin (MCH) 28.9pg, MCH concentration 30.7%, RDW-CV 14.6%. Corrected reticulocytes 5.16%, Ret-He 22.6, IPF 54.17%. Peripheral blood smears normochromic, normocytic, blast not found, platelets are rare. The diagnosis is menometrorrhagia with anemia due to bleeding caused by ITP. The patient was given PRC and platelet transfusion, methylprednisolone. Three months later, the patient had another prolonged menstruation, hair loss, no petechiae, or purpura. Laboratorium: Hb 8.2 g/dL, leukocytes 7800/uL, platelets 6000/uL, RBC 1.59 million/uL, MCV 94.3fL, MCH 28.9pg, corrected reticulocytes 5.08%, Ret-He 24.6, IPF 54.5%, ANA test positive, Anti dsDNA-NcX 190.2 IU/ml. The diagnosis is SLE. During the last 16 months, the patient took 10 mg prednisone with a platelet count >150,000/uL.

CONCLUSION: In any case of ITP in a child, consider the possibility of SLE.

Introduction

Immune thrombocytopenia (ITP) can precede the onset of systemic lupus erythematosus (SLE) by months to years. The incidence of pediatric ITP is 4.3/100,000 people/year [1]. The incidence of SLE in patients with ITP and the potential relationship between them is still unclear. Zhu et al. reported that SLE incidence in ITP patients and SLE incidence in non-ITPs was 4.7% and 0.19%, respectively. ITP patients had a 26-fold risk of developing SLE than the control group in the population. Furthermore, men have a lower risk of developing SLE than women [2].

Case Presentation

A 12-year-old girl weighing 46 kg came to the hospital with the complaint of 12 days-massive menstrual bleeding. Previously the patient had frequent nosebleeds. On physical examination, the patient is conscious, weak, pale. Eyes, ENT, heart, lungs, abdomen: within normal limits, no petechiae. On laboratory tests: Hb 4.6 g/dL, leukocytes 12,930/uL, platelets 11,000/uL, hematocrit 15%, Diff Count: basophils 0%, eosinophils 0%, stems 1%, segments 71%, lymphocytes 24%, monocytes 4%. Red blood cell (RBC) 1.59 million/uL, mean corpuscular volume (MCV) 94.3fL, mean corpuscular hemoglobin (MCH) 28.9pg, MCH concentration (MCHC 30.7%), RDW-CV 14.6%. Corrected reticulocytes 5.16%, Ret-He 22.6, IPF 54.17%. Peripheral blood smears normochromic, normocytic, blast not found, platelets are rare. The diagnosis is menometrorrhagia with anemia due to bleeding caused by ITP. The patient was given PRC and platelet transfusion, 50 mg of methylprednisolone intravenously every 12 h for 3 days, followed by 30 mg intravenous for 4 days. The patient went home in good condition. The patient lost to follow-up.

Three months later, the patient had another prolonged massive menstruation, appeared Malar rash on the cheeks, and hair loss in several places on the head. On the skin, there is no petechiae or purpura. Laboratory examinations: Hb 8.2 g/dL, leukocytes 7800/uL, platelets 6000/uL, hematocrit 25.1%, Diff Count: basophils 0%, eosinophils 5%, stems 1%, segments 60%, lymphocytes 29%, monocytes 5%. RBC 1.59 million/uL, MCV 94.3fL, MCH 28.9pg, MCHC 30.7%, RDW-CV 14.6%. Corrected reticulocytes 5.08%, Ret-He 24.6, IPF 54.5%. Urinalysis within normal limits.
The patient was given 4 × 250 ml PRC transfusion, 2 × 10U platelet transfusion, 50 mg of methylprednisolone intravenous every 12 h for 3 days, followed by 30 mg intravenous for 4 days. Immunology examination: ANA test titer 1:1000 (negative < 1:100). Anti dsDNA-NcX 190.2 IU/ml (negative < 100). The diagnosis is SLE. Furthermore, during the past 16 months, the patient took prednisone 2 × 1 tablet with a platelet count >150,000/µL. When the prednisone dose is lowered, it will cause the cheeks’ redness, an uncomfortable stomach, and weakness.

**Discussion**

Initially, the patient was diagnosed with newly ITP based on 12 days-massive menstrual bleeding, platelets of 11,000/µL, and platelets on the peripheral blood smear were rarely found. Hb 4.6 g/dL means that there has been a lot of blood loss, which is undoubtedly life-threatening. Therefore, the therapy is given PRC transfusion and platelet transfusion, followed by 2 mg/kg body weight of methylprednisolone for 7 days. This therapy suits the theory that if there is life-threatening bleeding and the platelets are <30,000/µL, we should give platelet transfusions and methylprednisolon as first-line ITP drugs [3], [4]. Patients are not given IVIG because it is expensive; the patient’s family cannot afford it. When the patient went home, he was given prednisone, but unfortunately, the patient lost to follow-up. We do not know whether this patient will develop persistent/chronic ITP, but the likelihood of developing chronic ITP is high. ITP in children ≥120 months, 47% will be chronic ITP [5]. Jung et al. stated that 85.9% of pediatric ITP would be in remission, and 14.1% of cases will become chronic ITP; the prognostic factor for chronic ITP is the older child’s age [6]. Makis et al. stated that a person’s prognostic factor in developing chronic ITP is age >10 years [7].

Three months later, the patient experienced massive menstrual bleeding accompanied by a Malar rash on the cheeks (butterfly appearance) and hair loss in several places on the head. With clinical findings in vaginal bleeding, Malar rash on the cheeks, hair loss, platelets of 6000/µL, the patient is suspected of having SLE. It turned out that the ANA examination was confirmed positive, and anti-dsDNA-NcX was positive. Based on the SLICC criteria to determine SLE’s diagnosis, which requires the fulfillment of ≥4 criteria out of 17 criteria with at least one clinical or laboratory criterion being met and at least one immunological examination criteria met, this patient was diagnosed with SLE. SLE criteria, according to SLICC, can be seen in Table 1 [8].

The mechanism by which ITP becomes SLE is not known. There are two principal causes of ITP: megakaryocyte maturation disorder, insufficient platelet production, and antibody-mediated platelet destruction exceeding bone marrow compensatory capacity. For ITP of autoimmune etiology, the glycoproteins (GP) expressed on the platelet surface (mainly GPIIb/IIIa and Ib/IX) are recognized by the immune system as foreign antigens, leading to the generation of autoantibodies. The subsequent interaction between the Fc segment of the autoantibody and Fc gamma receptor (FcyR) on the macrophage surface results in platelet destruction through phagocytosis [9]. Analyses have shown an increased frequency of antiplatelet antibodies in SLE patients with thrombocytopenia compared with SLE patients without thrombocytopenia. Antithrombopoietin receptor antibodies have been detected in higher frequency in patients with SLE who have thrombocytopenia than those who do not have a low platelet count [10], [11], [12], [13], [14].

Thrombocytopenia is a poor prognostic factor in SLE [15]. Thrombocytopenia is a frequent clinical manifestation of SLE [16]; 3–16% of ITP patients become SLE [17]. Zhao et al. reported that ITP initiated 12.8% of cases of SLE [18]. Hazzan et al. reported that of 222 ITP patients, under a 4.2-year follow-up, 3.6% developed SLE, all of which were women, mean age 12.7 years, with positive ANA [19]. In contrast Altintas et al., none of the ITP children with positive ANA developed SLE [20].

After the SLE diagnosis was established, the patient was motivated to remain in control of the doctor and regularly take prednisone medication. The patient was given a dose of prednisone full-dose, and because the platelet count was still >150,000/µL, the prednisone drug was tapering off gradually. The lowest attainable and effective prednisone dose that does not cause clinical symptoms anymore is 10 mg. Because once the prednisone dose is lowered, the cheeks’ redness develops, and the patient feels weak. Up to 16 months of monitoring, the patient can be clinically controlled with a prednisone dose of 10 mg with a thrombocyte count >150,000/µL.

**Table 1: SLICC Classification Criteria [8]**

| Clinical criteria                          | Immunologic criteria |
|-------------------------------------------|----------------------|
| Acute cutaneous lupus                     | ANA                  |
| Chronic cutaneous lupus                   | Anti-DNA             |
| Oral or nasal ulcers                      | Anti-Sm              |
| Non-scarring alopecia                     | Antiphospholipid Ab  |
| Arthritis                                 | Low complement       |
| Serositis                                 | Directs Coombs’ test |
| Renal                                     | in the presence of   |
|                                           | hemolytic anemia     |

| Neurologic                                | Hemolytic anemia     |
|-------------------------------------------|----------------------|
| Hemolytic anemia                          | Renal                |
| Leukopenia                                | Thrombocytopenia     |

(≤100,000/mm³)

SLICC: System Lupus International Collaborating Clinics. Requirements: ≥ 4 criteria (at least 1 clinical and 1 laboratory criteria) OR biopsy-proven lupus nephritis with positive ANA or Anti-DNA.
glucocorticoids, IVIG, anti-D immunoglobulin. Suppose first-line treatment fails (clinical manifestations and thrombocytopenia can not be controlled with in 3–6 months of therapy); in that case, it is necessary to think about treatment with second-line drugs, namely rituximab and thrombopoietin receptor agonists (TPO-RA, such as eltrombopag, romiplostim, and avatrombopag). If second-line drugs are also ineffective, third-line drugs can be used, such as fostamatinib, oseltamivir, atorvastatin [21], [22], [23], low doses of decitabine [24], hydroxychloroquine [25], [26], [27], azathioprine [28], mycophenolate mofetil [29], cyclosporine A [29], and tacrolimus [30].

**Conclusion**

In every case of ITP in a child, consider the possibility of SLE. We have to check the ANA test as a screening.

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