In conclusion, we identified a rare case of MDS/MPN-RS-T with a triple SF3B1/CALR/JAK2 mutation. The presence of multiple mutations is rarely observed, and the molecular mechanisms causing molecular complexity and their consequent clinical impact is unclear. We believe that this report contributes to a better understanding of the clinical features and molecular basis of this rare type of MDS/MPN-RS-T.

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Received on May 20, 2022; Revised on Jul. 4, 2022; Accepted on Jul. 8, 2022
https://doi.org/10.5045/br.2022.20222105

Acknowledgments
This study was supported by the Soonchunhyang University Research Fund (2022) and the National Research Foundation of Korea (NRF) grant, funded by the Ministry of Science and ICT (2021R1C1C1005725).

Authors’ Disclosures of Potential Conflicts of Interest
No potential conflicts of interest relevant to this article were reported.

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A rare case of pediatric immune thrombocytopenia with secondary antiphospholipid syndrome in Korea

TO THE EDITOR: Chronic immune thrombocytopenia (ITP) is defined as thrombocytopenia that persists for more than 12 months [1, 2]. In most cases, childhood ITP resolves spontaneously within 6 months [2]. However, approximately 20-30% of the children diagnosed with ITP develop chronic ITP [2]. Although ITP is a relatively common disease in childhood, chronic ITP in children must be carefully evaluated for its underlying cause. Risk factors for chronic ITP in children include older age at the time of ITP diagnosis, less severe thrombocytopenia, slow onset of symptoms, gradual improvement in platelet count at 4 weeks, and insufficient evidence of prior infection or vaccination [2]. Approximately 20% of ITPs are related to an underlying disorder and are classified as secondary ITPs [2]. In such cases, physicians should carefully reanalyze the patient’s history. Furthermore, bone marrow aspiration should be performed, and peripheral blood smears should be retested [1]. Secondary causes of ITP in children include systemic autoimmune diseases, infections, lymphoproliferative disorders, or immunodeficiency [3]. Systemic autoimmune diseases include systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS), rheumatoid arthritis, and autoimmune thrombocytopenia (e.g., Evans syndrome) [3]. Since APS is one of the causes of secondary ITP, patients with chronic ITP should be tested for APS [3]. However, there is little data on APS as an underlying cause of chronic ITP in pediatric patients. Herein, we report the case of an 11-year-old female Korean patient with chronic ITP, who was eventually diagnosed with APS at 15 years of age. This study was approved by the Institutional Review Board of Keimyung University Dongsan Hospital (approval no. 2022-03-028) and was conducted in accordance with the Declaration of Helsinki.
At the age of 11 years, the patient visited the pediatric hematologic clinic complaining of easy bruising and petechiae over the entire body for 1 week. She had no specific past or family history of autoimmune diseases. Laboratory tests revealed white blood cell (WBC) count of 6.93×10^9/L, hemoglobin of 12.6 g/dL, and platelet count of 11×10^9/L; while, all other results were within the normal range. The patient was administered 2 g/kg of intravenous immunoglobulin leading to increase in platelet count to 42×10^9/L. After discharge, the patient was prescribed oral prednisolone for the recurrent ITP. As the patient had persistent thrombocytopenia for more than 1 year, she was evaluated for underlying causes of secondary ITP. As for the evaluation of autoimmune diseases, laboratory findings detected the presence of antiphospholipid antibodies [lupus anticoagulant, anti-cardiolipin antibody, and anti-beta-2-glycoprotein I (anti-β2GP1) antibody]. Follow-up laboratory testing after 12 weeks also revealed positive results for lupus anticoagulant, anticardiopilin antibody, and anti-beta2GP1 antibody. Although the exact diagnostic criteria for pediatric APS have not been established, we suspected the possibility of APS based on the clinical features of APS including thrombosis and the presence of antiphospholipid antibody. We explained to the patient and her guardian that thrombosis may occur in the future as well. We also explained the symptoms that may occur based on the location of thrombosis. Subsequently, the corticosteroid dose was gradually reduced, considering the recurrence of thrombocytopenia. She was taking oral prednisolone 2.5 mg every other day, and her platelet count was maintained above 150×10^9/L since she was 13-years-old.

When the patient was 15-years-old, she presented to the outpatient clinic complaining of swelling and pain in her right lower leg for a week. Deep vein thrombosis (DVT) was initially suspected based on the patient’s history and underlying disease. She was transferred to the emergency department and underwent blood and imaging work-up. Laboratory tests revealed WBC count of 6.45×10^9/L, hemoglobin of 10.7 g/dL, platelet count of 163×10^9/L, prothrombin time of 13.5 sec (INR 1.18), fibrinogen of 276.7 mg/dL, antithrombin III level of 102.0%, fibrin/fibrinogen degradation product of 0.6 mcg/mL, prolonged activated partial thromboplastin time of 43.5 sec (normal range, 26-37 s), and D-dimer level of 1.33 mcg/mL. Follow-up laboratory findings also revealed the presence of antiphospholipid antibodies. Computed tomography (CT) angiography of the extremities revealed a focal filling defect in the right superficial femoral vein suggesting DVT (Fig. 1A). Venous duplex ultrasonography of the lower extremity revealed occlusion of the right superficial femoral vein with presence of collateral veins (Fig. 1B). To evaluate the presence of thrombi in other parts of the body, magnetic resonance angiography of the brain, pulmonary thromboembolism CT, and 2-dimensional echocardiography were performed. No thrombus formation other than DVT was observed in the right lower leg. Anticoagulant therapy with low-molecular-weight heparin (enoxaparin) was initiated. Subsequently, the swelling in her legs improved and the pain was relieved. After the symptoms were relieved, the patient was discharged with a prescription for direct oral anticoagulants (rivaroxaban, inhibitors of factor Xa). After 3 months of anticoagulation therapy, follow-up duplex ultrasonography showed improvement in DVT (Fig. 1C). Currently, the patient is being followed-up at the outpatient clinic with continuous oral anticoagulants and 20 mg of rivaroxaban daily.

APS is a systemic autoimmune disease that causes thrombosis and pregnancy morbidity with consistent positive antiphospholipid antibodies [4, 5]. APS can be primary or secondary, in conjunction with another autoimmune disease [5]. Although secondary APS is typically associated with SLE, other autoimmune conditions can also be associated with APS [6]. In an international registry study involving 121 pediatric patients with APS, 60 had secondary APS associated with autoimmune conditions [6]. Among them, 46 cases were associated with SLE (76.7%), 4 with SLE-like disease (7.7%), 4 with autoimmune thyroiditis (7.7%), 2 with rheumatic fever (3.3%), and only 1 each (1.7%) with ITP, hemolytic uremic syndrome, pauci-immune glomerulonephritis, and Behcet disease [6]. In the present case, further laboratory tests for SLE were periodically performed.

![Fig. 1](https://example.com/image1.png)  
**Fig. 1.** Computed tomography (CT) angiography and venous duplex ultrasound of the lower extremity in a pediatric patient with secondary antiphospholipid syndrome associated with immune thrombocytopenia. (A) In the lower extremity CT, a small focal filling defect (white arrow) was observed at the right distal superficial femoral vein suggesting deep vein thrombosis (DVT). (B) In the venous duplex ultrasound of the lower extremity, occlusion of the branch of right femoral vein and collateral veins was observed. (C) After 3 months of anticoagulation, follow-up duplex ultrasound showed improvement of DVT.
but no abnormalities were noted. Thus, the present pediatric patient can be considered a rare case of secondary APS associated with ITP.

As per the 2006 revised international consensus on APS classification criteria, APS can be diagnosed if the clinical and the laboratory criteria are satisfied [7]. Clinical criteria include confirmed vascular thrombosis episodes and pregnancy morbidity; one of these criteria must be met [7]. The lupus anticoagulant, anti-cardiolipin antibody, or anti-β2GPI antibody should be present on two or more occasions when tested at least 12 weeks apart, based on the laboratory criteria [7]. However, the diagnostic criteria of pediatric APS have not been established yet [4, 5]. Children with APS may show additional manifestations, including hematologic or neurologic abnormalities [5]. Furthermore, some pediatric patients with APS present only with positive antibodies and no clinical manifestations [5]. The mean age of onset of pediatric APS is 10.7 years [4]. The main feature of APS in children is venous thrombosis, with DVT of the lower extremities being the most common occurrence [5]. Non-thrombotic manifestations, including hematologic abnormalities such as Evans syndrome, isolated thrombocytopenia, autoimmune hemolytic anemia, leukopenia, and neurologic disorder including cholera are also noted in children with APS [5]. A recent Korean epidemiological study revealed a total of 3,088 newly diagnosed APS cases between 2009 and 2016 [8]. The mean age at APS diagnosis in Korea is approximately 45 years, and pediatric APS is very rare [8]. The epidemiology of pediatric APS remains largely undefined [5]. As pediatric APS is an unfamiliar and rare diagnosis, it is possible that pediatric APS is underdiagnosed, especially in the absence of children-specific diagnostic criteria [5].

The presence of antiphospholipid antibodies is not always related to the development of APS [9]. Due to its low sensitivity and high inter-laboratory variability, antiphospholipid antibody testing is not routinely performed in patients with chronic ITP [3]. However, in a prospective cohort study on antiphospholipid antibodies and APS in patients with ITP, APS developed in a significant number of patients with ITP who were initially positive for the antiphospholipid antibodies [9]. These patients showed clinical features of APS, such as thrombosis or fetal loss, after 38 months of follow-up [9]. According to this study, the continued presence of antiphospholipid antibodies in patients with ITP is an important risk factor for development of APS [9].

In conclusion, this is the first report of a Korean pediatric patient who developed APS after an initial diagnosis of chronic ITP. In the present case, an 11-year-old patient presented with thrombocytopenia. The thrombocytopenia persisted for over 1 year; hence, we investigated the underlying cause, and the results were positive antiphospholipid antibodies. Considering the persistent presence of positive antiphospholipid antibodies in the patient, we suspected the possibility of APS. Furthermore, the patient and her guardians were instructed to visit the hospital immediately if APS symptoms developed. Therefore, prompt treatment was possible when the patient developed symptoms of thrombosis.

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Received on Mar. 29, 2022; Revised on May 24, 2022; Accepted on Jul. 28, 2022
https://doi.org/10.5045/br.2022.2022074

Authors’ Disclosures of Potential Conflicts of Interest
No potential conflicts of interest relevant to this article were reported.

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