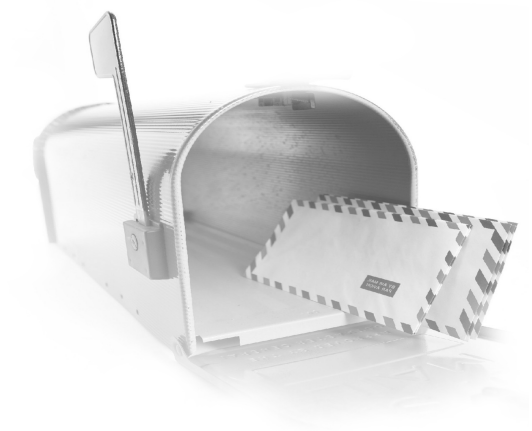

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Letters to the Editor

A case of immune thrombocytopenia associated with invasive thymoma successfully treated with eltrombopag

TO THE EDITOR: The thymus plays a vital role in cell-mediated immunity by producing functional T cells and inducing self-tolerance. As such, benign or malignant tumors originating from the thymus can lead to loss of self-tolerance and development of autoimmunity [1]. The most common autoimmune disease associated with thymic tumor is myasthenia gravis, followed by pure red cell aplasia (PRCA) [2]. There are reports of other types of immune cytopenias including immune thrombocytopenia [3] and acquired amegakaryocytic thrombocytopenia (AAMT) [4], but because of their rare incidence, the treatment is not well defined. Since thrombocytopenia can cause adverse consequences, patients with low platelet count require prompt clinical attention. Here, we report the case of a patient with invasive thymoma and associated immune thrombocytopenia successfully treated with eltrombopag, a thrombopoietin receptor agonist.

A 69-year old male patient with no significant previous medical history presented to the emergency department with dyspnea. He had been experiencing intermittent edema in the upper extremities for the preceding 3 months but did not seek any medical attention for the symptoms. The chest X-ray taken upon arrival showed cardiomegaly with bilateral pleural effusion. The patient was admitted for further evaluation and echocardiography and chest computed tomography (CT) were undertaken. The images revealed heterogeneous soft tissue enhancing mass in the mediastinum infiltrating the transverse sinus and right para-tracheal area, associated with severe narrowing of superior vena cava, bilateral pleural effusion, and a significant amount of pericardial effusion causing cardiac tamponade (Fig. 1A). There were no other organ involvements. His complete blood count showed marked thrombocytopenia (8×10^9/L) but normal hemoglobin level (12.2 g/dL) with no neutropenia (white blood cell, 6.3×10^9/L). After platelet transfusion, pericardiocentesis was performed and dyspnea was relieved. Since the cytology performed with pericardial effusion did not any yield any pathological diagnosis, endobronchial ultrasound biopsy was performed and the World Health Organization (WHO) type B1 thymoma [5] was diagnosed. As the mass was encasing the heart and major vessels, neither operation nor radiation could be the therapeutic options, and thus, the patient was offered chemotherapy with cyclophosphamide, doxorubicin, and cisplatin (CAP) for the treatment. Since there were no other autoimmune diseases and the bone marrow examination obtained prior to chemotherapy showed no metastatic involvement (Fig. 2A), thymoma was thought to be the primary cause of thrombocytopenia.

After the first cycle of chemotherapy, his platelet count recovered to around 50×10^9/L. The edema subsided and the patient was subjectively feeling better. Consequently,

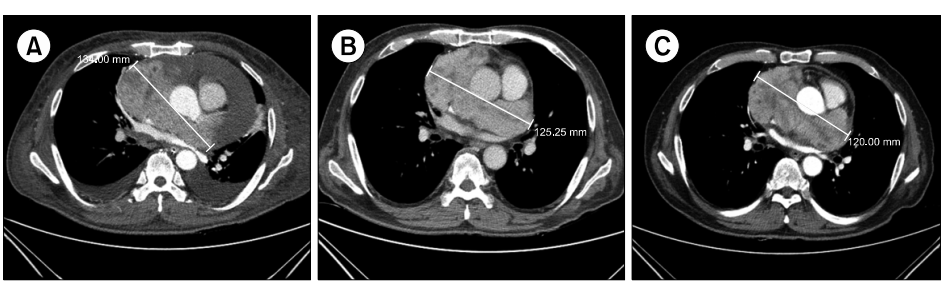

Fig. 1. Chest computed tomography **(A)** at diagnosis, **(B)** after three cycles of CAP, and **(C)** six months after completion of chemotherapy.

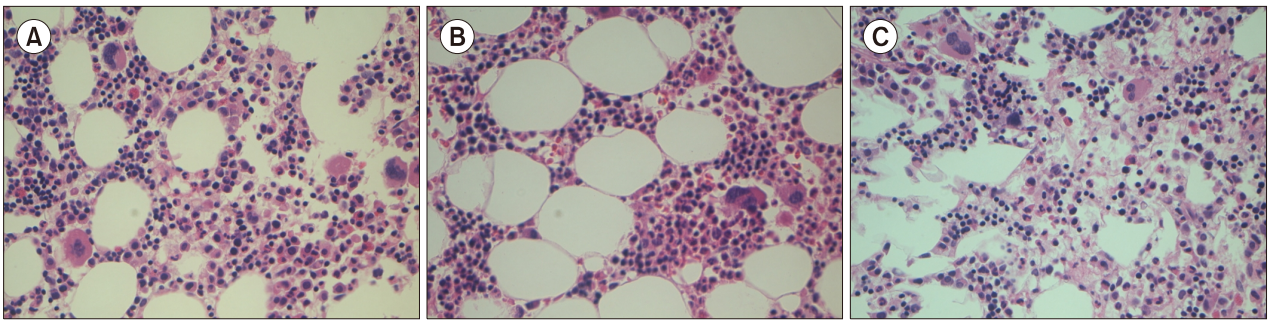

Fig. 2. **(A)** Picture of bone marrow at diagnosis. The section shows normocellular marrow without malignant tumor cells (H&E stain, ×400). **(B)** Second bone marrow examination was performed before the third cycle of chemotherapy. The section (H&E stain, ×400) showed nearly normal distribution of nucleated cells without infiltrative tumor cells. **(C)** Final bone marrow examination was performed before administration of eltrombopag. The section (H&E stain, ×400) shows normocellular marrow with slightly increased megakaryocytes (right side).

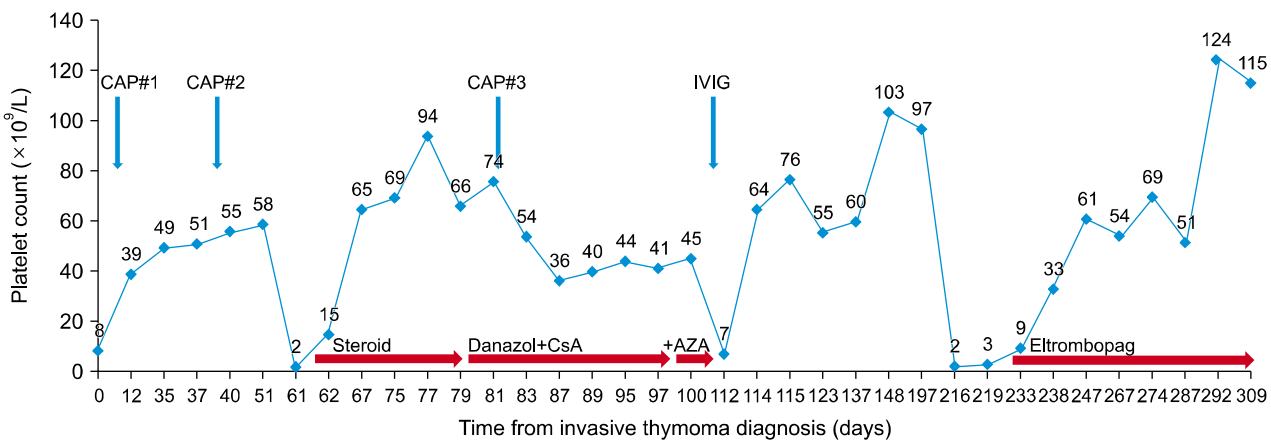

Fig. 3. Treatment course and serial platelet counts.

the second cycle of CAP was administered. On the 10th day of follow-up, his platelet count was 58×10^9/L without other cytopenias. A repeat CT scan was undertaken to evaluate the tumor response, and it showed a reduced size of the mediastinal mass (Fig. 1B).

When the patient visited the clinic for the third cycle of CAP, his platelet count, however, was again low (2×10^9/L) and he complained of hematochezia. He was immediately admitted for further evaluation. When no recovery in the platelet count was seen after a week of supportive therapy, a second bone marrow examination was performed (Fig. 2B). The bone marrow aspirate at this point showed an adequate number of erythropoietic cells, granulopoietic cells, and megakaryocytes without dysplasia. The bone marrow biopsy showed normocellular marrow areas (30%) and some acellular areas (<10%). Based on these findings, chemotherapy-induced marrow suppression super-imposed on thymoma-associated immune cytopenia was assumed. Prednisolone was started at a dose to treat immune thrombocytopenia (1 mg/kg). After delaying the chemotherapy for 2 more weeks, his platelet count was found to be 69×10^9/L and he underwent the third cycle of CAP with a 30% reduced dose. After 3 weeks of steroid treatment, he developed steroid-induced myopathy and diabetes mellitus. The steroid was tapered off and cyclosporine plus danazol was initiated. The platelet count level remained somewhat stable ranging from $30–50\times10^9$/L, but due to the unpredictable hemogram picture and indolent nature of his tumor, chemotherapy was put on hold indefinitely.

After a month of danazol plus cyclosporine treatment, the patient developed disabling intention tremor preventing him from feeding or dressing by himself. As replacement therapy, azathioprine was administered but his platelet count dropped below 7×10^9/L, and he was again admitted with massive hematochezia. Despite the low WBC and platelet counts, the reticulocyte count was normal. Intravenous immunoglobulin (IVIG) was initiated for the management of immune thrombocytopenia. IVIG showed immediate effects, and the platelet count increased to 76×10^9/L.

The hemogram picture and the tumor remained stable

for 2 months (Fig. 1C). The patient, however, again presented to the emergency department with hematochezia and severe thrombocytopenia (platelet count, 2×10^9/L), which were refractory to IVIG treatment. He underwent a bone marrow examination for the third time, and at this point, the marrow showed normal cellularity (30%) with slightly increased megakaryocyte (Fig. 2C). With an affirmative diagnosis of immune thrombocytopenia, eltrombopag was administered at a dose of 25 milligrams (mg) as per recommendation and then increased to 50 mg after 2 weeks of suboptimal response. With a dose of 50 mg, the platelet level was stabilized within 2 weeks and was normalized in another 6 weeks. He is currently on eltrombopag 50 mg and the platelet count is normal and no significant adverse effects of the drug were observed (Fig. 3).

The association of thymic tumors with autoimmune disorders is well-established. It has been reported that up to 30% of patients with thymoma develop autoimmunity during the course of their disease [6]. Cases of autoimmune hematologic phenomena have also been described, most well-known being PRCA [7]. Although in a lesser frequency other hematologic manifestations, such as thrombocytopenia has also been documented. Several mechanisms can cause thrombocytopenia in thymoma, such as 1) secondary to aplastic anemia [8]; 2) immune thrombocytopenia [3, 9]; and 3) acquired amegakaryocytic thrombocytopenia [4]. As immune thrombocytopenia seems to be a rare occurrence in this context [2], there is a lack of a standard treatment for this potentially life-threatening condition.

In previously reported cases of thymoma-associated immune thrombocytopenia, all patients were apt for thymectomy [2, 3, 9] and thrombocytopenia was improved after surgery. Unfortunately, in this case, the mediastinal mass was encasing the large vessels (Fig. 1A), thus the patient was deemed inoperable, and hence, systemic chemotherapy had to be administered. Initially, the patient responded well to chemotherapy, and experienced substantial improvement in the subjective symptoms as the size of the mediastinal mass was reduced. Regardless of the tumor response, the patient, however, developed severe thrombocytopenia in the absence of anemia or neutropenia. Based on the follow-up bone marrow examination, the patient was given immunomodulators (steroids, cyclosporine, azathioprine, and IVIG) usually used in thymoma-associated autoimmune disorders. These agents, however, either cause significant side effects which can compromise the quality of life of the patients or result in less-than-satisfactory outcomes. After all other treatment measures failed, and eltrombopag, a thrombopoietin receptor agonist, was initiated. The rationale of this decision was based on the immediately preceding bone marrow findings which shared typical characteristic features of idiopathic thrombocytopenic purpura (ITP), and the proven efficacy of eltrombopag in chronic ITP [10, 11]. The patient was administered eltrombopag 50 mg per day and the platelet count recovered without any further complications.

This is, to the best of our knowledge, the first documented use of eltrombopag in a patient with thymoma-associated immune thrombocytopenia, who was refractory to all other therapeutic measures. Our study also highlighted that flares of autoimmune phenomena do not necessarily correlate with the primary tumor response. Although rare, immune-mediated thrombocytopenia can occur in association with thymic tumors. Vigilant workups including bone marrow examination help in making the correct diagnosis leading to appropriate management and good prognosis. Eltrombopag can be useful even in immune thrombocytopenias caused by other underlying diseases in the background of other autoimmune disorders.

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No potential conflicts of interest relevant to this article were reported.

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Coexistence of *BCR/ABL1*-positive chronic myeloid leukemia and *JAK2 V617F*-mutated myelofibrosis successfully treated with dasatinib and ruxolitinib

TO THE EDITOR: Myeloproliferative neoplasms (MPNs) are clonal hematopoietic stem cell disorders characterized by the proliferation of cells of one or more of the myeloid lineages. Depending on the presence or absence of a *BCR/ABL1* translocation, they can be divided into *BCR/ABL1*-positive chronic myeloid leukemias (CMLs) and *BCR/ABL1*-negative MPNs, respectively [1]. Thus, by World Health Organization (WHO) criteria, primary myeloid fibrosis (PMF) cannot coexist with CML, as the exclusion of CML is one of the major criteria for PMF diagnosis. However, there are a few reports that have described the coexistence of the two diseases [2-4]. Herein, we report the case of a patient who initially presented with features of CML and PMF. He was treated with dasatinib, and soon after experienced aggravated constitutional symptoms as well as leukocytosis. Concomitant administration of ruxolitinib ameliorated his symptoms.

The 68-year-old man had visited our clinic with hematologic test abnormalities; that is, 28,710/μL for white blood cell (WBC) counts, 10.4 g/dL for hemoglobin, and 244,000/μL for platelet counts. A peripheral blood smear examination demonstrated an excess of myelocytes and metamyelocytes. Elevation of the serum lactate dehydrogenase (LD) level was also noted. His abdominal computed tomography (CT) scan demonstrated marked splenomegaly (22.7 cm).

Suspecting an MPN of mostly CML, a bone marrow examination was done. The cellularity was almost 100% and prominent granulopoiesis was noted. The megakaryocytes were high in number, and some of them showed atypia, such as decreased cytoplasm, cloud-like nuclei, and dense cluster formation (Fig. 1). A grade I-II fibrosis was observed. Regarding the cytogenetics, a *BCR/ABL1* translocation was observed in 9 out of 21 (42.8%) cells by chromosomal analysis and in 246 out of 400 (61.5%) cells by fluorescence *in situ* hybridization (FISH). The transcript level determined by real-time quantitative polymerase chain reaction (RQ-PCR) was 65.7% IS (international scale). In addition, a *JAK2-V617F* mutation was detected. These findings were sufficient for the diagnosis of CML. The patient was started on dasatinib 100 mg once daily on May 13, 2016. During the first 3 months of treatment, the patient had never achieved a complete hematologic response, as the leukocyte counts remained at around 15,000/μL.

In the bone marrow examination done at 3 months, atypical megakaryocytes were still noted as well as grade II fibrosis. A CT scan revealed the spleen size to be 20.9 cm. Suspecting treatment failure, the dasatinib was increased to 140 mg once daily. Five days later, a complete cytogenetic response test reported none of the 14 cells by chromosomal analysis and none of the 400 cells by FISH had the *BCR/ABL1* translocation. A major molecular response was also achieved (0.07% IS). When the patient visited the clinic 2 weeks later, he complained of constitutional symptoms, such as fever, poor oral intake, headache, and severe fatigue. Unexpected leukocytosis (37,860/μL) and anemia (7.9 g/dL) were noted. He was started on hydroxyurea to ameliorate his leukocytosis, and the dasatinib was reduced to 100 mg once daily. Two weeks later, his WBC count had decreased and his symptoms also improved. Because hydroxyurea worsened his anemia, he had taken it temporarily, and when he stopped it, the WBC count increased. At the 6-month evaluation, the bone marrow findings were not significantly different from the previous findings. The spleen size had decreased slightly to 18.8 cm. Complete cytogenetic and molecular (0.00% IS) responses were also sustained. Despite these responses, the patient had been dependent on hydroxyurea for control of the symptoms and leukocytosis.

We assumed that both CML and PMF clones existed, and suppressing the CML clones may have stimulated the PMF clone, which resulted in leukocytosis and aggravation of the constitutional symptoms. Thus, on December 9, 2016, the patient started to take ruxolitinib 20 mg twice daily concurrently with dasatinib. At this time, his MPN10 score was 62, and the international prognostic scoring system (IPSS) group was high-risk owing to his age, symptoms, and leukocytosis. The leukocytosis resolved after 2 weeks, and so did the constitutional symptoms. In March 2017, after 3 months of ruxolitinib treatment, the MPN10 score improved to 26 and the spleen size decreased to 16.7 cm.