Secondary Chronic Immune Thrombocytopenia in Diffuse Large B-cell Lymphoma: A Rare Case Report

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Abstract

Objective: To present a case of rare secondary chronic immune thrombocytopenia in diffuse large B-cell lymphoma.

Methods: A case of secondary ITP associated with diffuse large B-cell lymphoma (DLBCL) in a 58-year-old woman suffering from hemorrhagic tendencies that was refractory to conventional treatments of ITP was reported. This case is a rarity because there are not many cases of secondary chronic ITP due to DLBCL have been reported to date.

Results: A 58-year-old woman was diagnosed with ITP around 11 months before she was admitted to the Emergency Room with bleeding. Previous treatment with steroid and azathioprine was only temporarily effective. During the course of treatment, splenomegaly and lymphadenopathy were identified, but lymph node biopsy was delayed by the thrombocytopenia. The drug was then replaced to the eltrombopag, which showed good response. However, the patient had to undergo splenectomy because of the mechanical effect of splenomegaly, with the biopsy result showed DLBCL. Immune thrombocytopenia then went into a complete remission after splenectomy.

Conclusion: In cases of ITP that are refractory to conventional treatments, a thorough search for secondary ITP might be helpful, even if no underlying disorder is detected at the initial presentation.

Keywords: Diffuse Large B-Cell Lymphoma, refractory, secondary immune thrombocytopenia, splenectomy

Introduction

Immune thrombocytopenia (ITP) is a bleeding disorder characterized by isolated thrombocytopenia (platelet count <100,000/µL), and can be caused by various etiologies.[1] Primary ITP is idiopathic, whereas secondary ITP is linked to an underlying condition.[2] It has been reported that approximately 20% of cases of ITP are associated with underlying factors, such as other autoimmune diseases, drugs, viral infections, or Helicobacter pylori infection. In cases of ITP that are refractory to conventional treatment, a thorough search for secondary ITP might be helpful, even if no underlying disorder is detected at the initial presentation.[3]

This study presented a rare case of secondary ITP associated with Diffuse Large B-Cell Lymphoma (DLBCL) in a 58-year-old woman which was refractory to conventional treatments of immune thrombocytopenia.

Case

A 58-year-old woman was admitted to our hospital Emergency Room (ER) in March 2020 due to oral mucosal bleeding accompanied by a red skin rash, bruised skin, and red-coloured urine that appeared three days prior to the patient's admission.

Eleven months before the ER admission,

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she came to our Hematology outpatient clinic with oral mucosal bleeding. She had been receiving treatment for ITP from another hospital with methylprednisolone for six months. The steroid was then tapered down and azathioprine 50 mg was added. One week later, her platelet count had increased from 34,000/μL to 58,000/μL and Immature Platelet Fraction was 7,9. The diagnosis remained and the treatment of methylprednisolone 4 mg and azathioprine 50 mg were continued.

Two months before the ER admission, the patient came to Hematology outpatient clinic again with left upper quadrant abdominal pain. A physical examination revealed splenomegaly (Schuffner I), and an abdominal ultrasonography examination confirmed a splenomegaly of 8x5x6 cm. We still considered ITP diagnosis even though other causes were still possible, and more examinations were planned to look for secondary causes. The Antinuclear Antibody (ANA) test was negative. She continued methylprednisolone and azathioprine, and 2 weeks later the platelet count increased to 81,000/μL. Methylprednisolone was then stopped, while azathioprine was continued.

A chest Computed Tomography (CT) with contrast that had been done prior to ER admission showed right superior and inferior paratracheal lymphadenopathy and left supraclavicular lymphadenopathy with the largest size ± 1.1 x 1.3 x 1 cm in the left supraclavicle. Lymphoma or tuberculosis was suspected as the underlying disease. She was referred to a surgical oncologist for an excisional biopsy of the lymph node, but by then her platelet count had decreased to 2,000/μL and bleeding occurred, so eventually she was sent to our ER.

A physical examination on the day of hospitalization showed that her vital signs were stable. She was anemic with petechiae on her skin and oral mucosal bleeding was identified. The lymph nodes in the neck were not palpable. An abdominal examination revealed splenomegaly (Schuffner III). Laboratory examinations showed pancytopenia with a hemoglobin level of 8.9 g/dL, a leukocyte count of 2,800/μL, and a platelet count of 2,000/μL. A peripheral blood smear analysis revealed anisocytosis, some polychromasia, a normal leucocyte count without immature cells, and thrombocytopenia without giant platelets. There was microscopic hematuria.

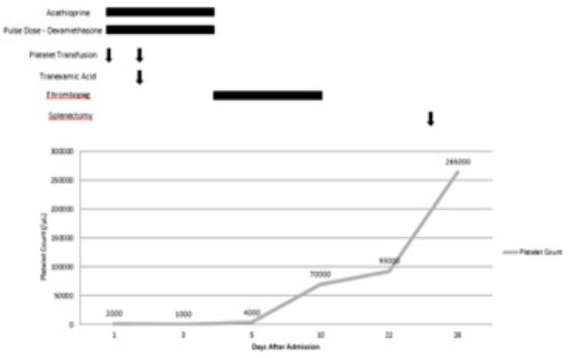

Fig. 1 The Patient's Clinical Course

She was treated with a pulse dose of dexamethasone (40 mg intravenously) daily for four days, 50 mg of azathioprine orally twice daily, and platelet transfusion until the platelet count >50,000/μL or until the bleeding stops. On the third day of hospitalization, the platelet count decreased to 1,000/μL. She underwent another abdominal ultrasonography on the fourth day of hospitalization which revealed a lymphadenopathy in the right para-iliac region with a diameter of ±1.74 cm. On the fifth day of hospitalization the platelet count was 4,000/μL. We stopped azathioprine and started giving her 25 mg of eltrombopag orally once daily. After the seventh day of eltrombopag, the platelet count was 70,000/μL. The patient was discharged on the tenth day of hospitalization and was scheduled to have an abdominal CT with contrast after discharged. The patient's clinical course can be summarised in Fig. 1.

The abdominal CT revealed multiple hypodense lesions, lobulated, conglomerated in paraaorta region and the enlargement of multiple inguinal lymph nodes bilaterally, suggestive of lymphoma and hepatosplenomegaly. The laboratory test twelve days after discharge revealed a platelet count of 93,000/μL.

Two weeks after discharge, the spleen size increased to Schuffner VI so the patient underwent a splenectomy in consideration of mechanical problems caused by the size of the spleen, pursuit of tissue histopathological diagnosis, and possible hypersplenism. Macroscopic and microscopic views of the spleen can be seen in Fig. 2A and 2B. A histopathological examination of the spleen revealed Diffuse large B-cell lymphoma with positive immunohistochemical (IHC) staining for expression of CD20, CD5, and Ki67 (positive >40%) but negative for expression of CD10. The microscopic view shows tumor mass consists of proliferation of small cells with follicular structure, clear cytoplasm and

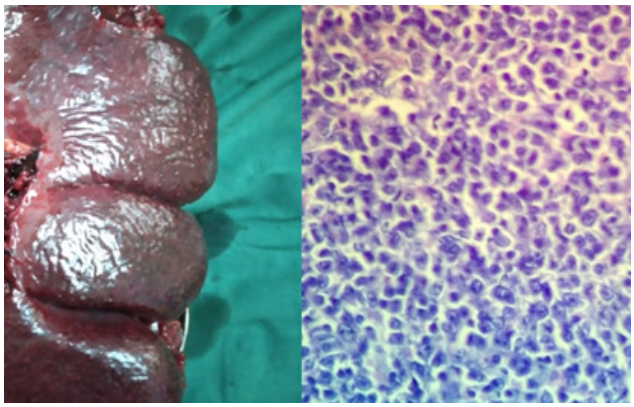

Fig. 2A. Macroscopic View of the Spleen; 2B. Microscopic View of the Spleen Shows Tumor Mass Consists of Proliferation of Small Cells with Follicular Structure, Clear Cytoplasm And Irregular Nucleus. Centrum germinativum infiltrated by small lymphoid cells. Sinuses and cords of Billroth are infiltrated by lymphoid cells

irregular nucleus. Centrum germinativum infiltrated by small lymphoid cells. Sinuses and cords of Billroth are infiltrated by lymphoid cells. Laboratory tests one day after the splenectomy showed a significant increase in the platelet count to 265,000/μL.

Microscopic view of the spleen shows tumor mass consists of proliferation of small cells with follicular structure, clear cytoplasm and irregular nucleus. Centrum germinativum infiltrated by small lymphoid cells. Sinuses and cords of Billroth are infiltrated by lymphoid cells.

The final diagnosis of the patient was stage IV high grade B-cell lymphoma (Diffuse large B-cell lymphoma) and Secondary Immune Thrombocytopenia (Lymphoma-associated).

Discussion

The incidence of ITP is estimated to be 2 to 5 per 100.000 persons in the general population.[4] Immune thrombocytopenia can manifest before, during, or after the diagnosis of lymphoma.5 Immune thrombocytopenia occurring prior to the diagnosis of aggressive DLBCL is rare.6 Ogata *et al*., 2019 revealed only 10 cases of DLBCL, which is the most common type of Non-Hodgkin lymphoma (NHL), complicated by ITP have been reported to date.[7] Tan *et al*. retrieved published papers from 1960 to 2010 and in three reported cases the ITP occurred 4, 18 and 46 months preceding DLBCL. In five cases ITP and DLBCL occurred concurrently.[6, 8]

Our case is ITP in a 58-year old women, slightly older than reported in previous studies which identified a median age of 50–55 years.[9] Our case presented with thrombocytopenia 11 months before her lymphoma diagnosis, similar to cases reported by Tan.6

Primary splenic DLBCL is very rare as it occurs in less than 1% of NHL. It is most commonly found in females and older males.[10] Shi *et al*., revealed that in 1,085 patients, 679 (62.6%) cases were nodal DLBCL (N-DLBCL) with the most common sites being the lymphonodus (64.8%), Waldeyer's ring (19.7%), the mediastinum (12.8%) and the spleen (2.7%).11

In previously untreated DLBCL, chemotherapy of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) remain the backbone of therapy, with the total number of cycles and addition of radiation dependent on the stage at presentation and tumour bulk. This approach can achieve durable remission in approximately 60% of patients.[12,13] R-CHOP is most often given in cycles 3 weeks apart.14

Khalid *et al*.[10] revealed that effective treatment options for massive splenomegaly include splenectomy, chemotherapy and/or radiation.A splenectomy not only releases the pressure on adjacent organs and solves the issues of hypersplenism, but it also provides a definitive histopathological diagnosis of the underlying cause. After a splenectomy, cytopenias resolve in most cases. Djokic *et al*.[15] revealed a case of a patient with resolved cytopenias in the weeks after the splenectomy.

The prognosis of DLBCL-associated ITP is still not fully understood because of only 10 cases being reported before. In most of these cases, the DLBCL-associated ITP was refractory to conventional treatments for

ITP, being refractory to steroid therapy in four cases.[16,17] In all ten cases, the patients underwent specific therapy for DLBCL.[3,6,16-18] In seven cases, the ITP went into remission after treatment.[3,19,20] Three patients underwent an additional splenectomy.[18,19,21] The splenectomy rather than the treatments for lymphoma might have been responsible for the remission seen in these cases. This case suggests that controlling the lymphoma can have beneficial effects on DLBCL-associated ITP. Our case develops ITP remission after a splenectomy without specific therapy for DLBCL. Ideally the patient was also given chemotherapy with R-CHOP regimen, which comprises rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone.[3] But our patient refused further treatment.

Our case report has some limitations, such as no BMAT carried out to assess the diagnosis of hypersplenism and bone marrow involvement, and no data on LDH level.

Diagnosis of lymphoma should still be considered as one of the underlying diseases for ITP in middle-aged patients, even if lymphoma symptoms are absent in the initial presentation. A thorough search for underlying disorders is important in cases of ITP that are refractory to conventional treatments. The precise pathogenesis of lymphoma-associated ITP needs further investigation.

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