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Case Report

Splenic Marginal Zone Lymphoma with Prominent Myelofibrosis Mimicking Triple-Negative Primary Myelofibrosis

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Keywords
SMZL · PMF · Differential diagnosis · Triple-negative · JAK2

Abstract
Myelofibrosis (MF) can occur due to a wide variety of causes including malignant lymphoma. We report a case of splenic marginal zone lymphoma complicated by MF mimicking primary myelofibrosis (PMF). The *JAK2*, *CALR* and *MPL* mutations are detected in more than 90% of PMF cases, and when detected, the diagnosis of PMF is usually straight forward. Mutational analysis should be done in all cases of MF, and in triple-negative cases, an exhaustive investigation of other causes of MF should be carried out before a diagnosis of triple-negative PMF is rendered.

Introduction

Splenic marginal zone lymphoma (SMZL) is an indolent B-cell lymphoma typically presenting with splenomegaly and no lymphadenopathy. As in other types of malignant lymphoma, SMZL can also be complicated by myelofibrosis (MF), and we demonstrate that in such cases it can mimic primary myelofibrosis (PMF) and is a potential diagnostic pitfall. PMF is

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classified as one of the Ph-negative myeloproliferative neoplasms (MPNs). The *JAK2*, *MPL* and *CALR* mutations are highly specific for MPNs, and the diagnosis of PMF is straight forward once one of the mutations are detected. On top of this, only 8.7% of PMF cases are reported to be negative for *JAK2*, *MPL* and *CALR* mutations (triple-negative). MF can develop due to a wide variety of reactive causes, and an exhaustive investigation should be carried out before a diagnosis of triple-negative PMF is rendered.

Case Report

A 71-year-old-man presented with general malaise and weight loss from May 2014, and he was referred to our department in June 2014 with a presumptive diagnosis of PMF from a local hospital. On admission, the spleen was enlarged and palpable 12 cm below the left costal margin. White blood cell (WBC) count was 1.0 × 10^9/L with 20.2% neutrophils, 45.2% lymphocytes, 20.2% monocytes, 10.6% eosinophils and 3.8% basophils. Hemoglobin (Hb) and platelet counts were 6.9 g/dL and 91 × 10^9/L, respectively. Total bilirubin was slightly increased at 1.89 mg/dL, serum haptoglobin was below 10 mg/dL and direct coomb's test was positive, and thus complication with autoimmune hemolytic anemia (AIHA) was diagnosed. Peripheral blood flow cytometry was unremarkable with no light chain restriction. A whole body computed tomography (CT) scan revealed marked splenomegaly but no lymphadenopathy (Fig. 1a). Bone marrow (BM) aspiration resulted in a dry tap, and BM biopsy revealed WHO-defined MF-2 with an increase of mature megakaryocytes (Fig. 1b). *JAK2*, *CALR*, and *MPL* mutations were analyzed as previously described but were negative [1], and the diagnosis was initially thought to be triple-negative PMF. However, because AIHA is often reported in conjunction with lymphoproliferative disorders, and soluble interleukin-2 receptor was found to be elevated at 4980 U/ml, we performed a CT-guided splenic needle biopsy to rule out lymphoma. Splenic biopsy revealed clustering of CD20-positive small lymphocytes which were negative for CD5, CD10, CD23, cyclinD1, SOX11, and LEF1 (Fig. 1c, d). Fluorescence in situ hybridization (FISH) analysis performed on paraffin-embedded tissue sections were positive for the *IgH* (14q32) split signal, and negative for *BCL2* (18q21), *BCL6* (3q27), *BCL10* (1p22), and *MALT1* (18q21) split signals. Thus, a diagnosis of SMZL was made. Starting in mid-August 2014, rituximab was administered weekly at a dose of 375 mg/m^2/day for 6 weeks resulting in a marked reduction of spleen size, improvement of pancytopenia, and he no longer needed red blood cell transfusions which were initially administered at approximately four units per week. The BM became aspirable, although BM biopsy still showed MF. Twelve additional bimonthly administrations of rituximab 375 mg/m^2/day were carried out in the following two years. The spleen was not palpable as of January 2015 and the complete blood count normalized. Relapse of SMZL was seen in October 2017, and pancytopenia and splenomegaly recurred. However, readministration of rituximab again lead the patient to a second remission.

Discussion/Conclusion

SMZL mainly involves the spleen, BM, and peripheral blood, but peripheral lymphadenopathy is uncommon. Complication with MF has been reported in a variety of non-Hodgkin lymphomas such as diffuse large B-cell lymphoma, intravascular large B-cell lymphoma, follicular lymphoma, mantle cell lymphoma, Burkitt lymphoma, lymphoplasmacytic lymphoma, angioimmunoblastic T-cell lymphoma, and peripheral T cell lymphoma, NOS, but there is only

one report of SMZL complicated with MF in the literature [2–7]. SMZL responds well to rituximab, and rituximab monotherapy has been reported to achieve an overall response rate of 92% and 5- and 10-year overall survival rates of 93 and 85%, respectively [8]. Our patient also responded well to rituximab and remains well without life-threatening pancytopenia, which would not have been achieved if he were to be erroneously diagnosed as PMF. Both SMZL and PMF can present with splenomegaly, pancytopenia, and MF, and the two entities can clinically mimic each other. The *JAK2*, *MPL*, and *CALR* mutations are highly specific for MPNs. Only 8.7% of PMF are reported to be absent for all three mutations and referred to as "triple-negative" PMF [9]. MF can occur due to a variety of causes other than PMF including, but not limited to, connective tissue disease, malignancies other than MPNs, specific infections and drugs, hyperparathyroidism, grey platelet syndrome, and rickets [10]. Thus, an exhaustive investigation for all other causes of MF must be carried out before a diagnosis of triple-negative PMF is rendered. In conclusion, all patients with MF should undergo examinations for *JAK2*, *MPL*, and *CALR* mutations, and in triple-negative cases, a careful and thorough exclusion of other causes of MF including SMZL is essential.

Statement of Ethics

The patient has given his informed consent to publish his case. Information revealing the subject's identity was avoided.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Miyuki Tsutsui drafted the manuscript and contributed on the interpretation of data. Hajime Yasuda revised the manuscript and contributed on the interpretation of data. Yasunori Ota performed the pathology analysis and contributed on the interpretation of data. Norio Komatsu revised the manuscript, contributed on the interpretation of data and gave final approval of the version to be published. All authors have read and approved the final manuscript.

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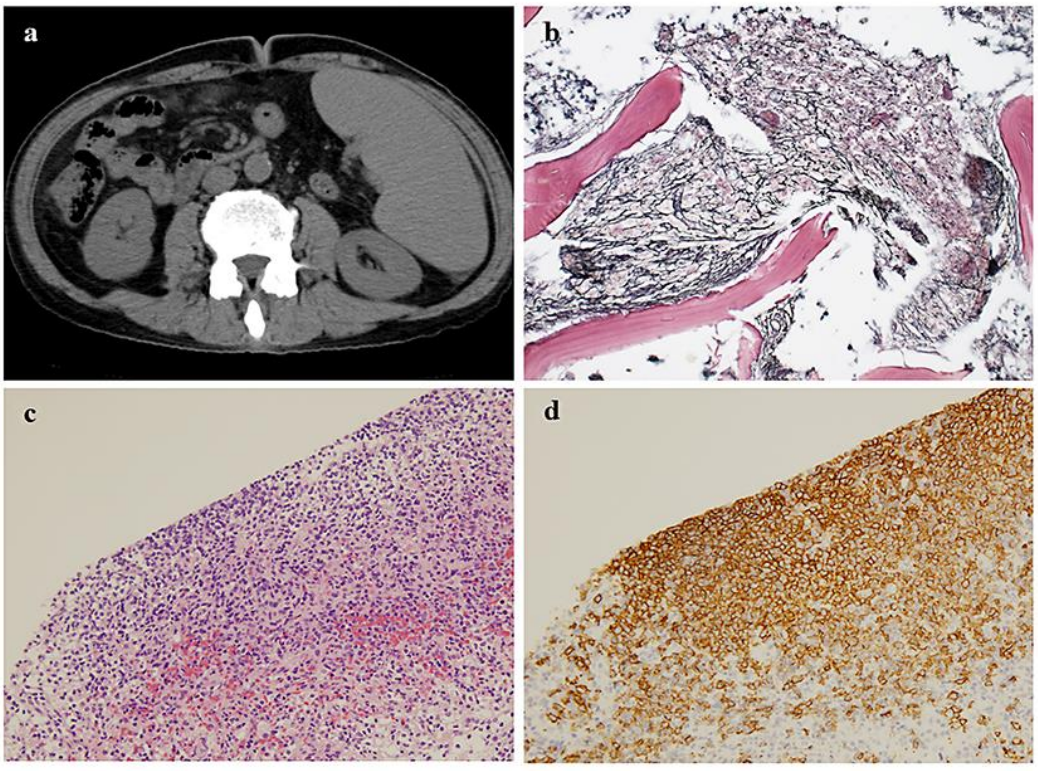

Fig. 1. CT image shows splenomegaly (**a**). Bone marrow biopsy sliver impregnation shows WHO-defined grade-2 myelofibrosis (**b**). Splenic needle-biopsy. Hematoxylin and eosin staining shows proliferation of small lymphocytes (**c**) which are positive for CD20 (**d**).