Autoimmune myelofibrosis associated with autoimmune hemolytic anemia successfully treated with ruxolitinib

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Research Article

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Abstract

A 55-year-old man suffered from dyspnea, general malaise, and jaundice. His laboratory data showed pancytopenia and hemolytic anemia, and computed tomography showed splenomegaly. Bone marrow examination revealed myelofibrosis (MF)-1. The hemolytic anemia was diagnosed as IgM autoimmune hemolytic anemia (AIHA) with negative direct and indirect Coombs test but positive IgM-direct antiglobulin test. We started ruxolitinib 20 mg, which improved not only bone marrow fibrosis, symptoms related to myeloproliferative neoplasms and splenomegaly, but also AIHA. AIHA may be associated with Autoimmune MF (AIMF), and cytokines such as transforming growth factor (TGF)- β are thought to be involved in such cases. This case suggests that ruxolitinib may improve the cytokine levels and may lead to the treatment of AIHA as well as AIMF.

Introduction

Autoimmune myelofibrosis (AIMF) is secondary MF associated with autoimmune diseases [1]. In many cases, single-agent prednisolone can induce blood cell recovery; however, few cases show complete improvement of fibrosis. We report the first case of rapid improvement of myelofibrosis and improvement of the autoimmune disease itself in a patient with AIMF treated with ruxolitinib monotherapy.

Case Presentation

A 55-year-old man presented with dyspnea, general malaise, and jaundice since 3 months that gradually worsened. Abdominal CT showed splenomegaly (Fig. 1a); laboratory tests showed pancytopenia (white blood count $2.2 \times 10^9/L$, hemoglobin 81g/L, platelet count $7.6 \times 10^9/L$, reticulocyte count 0.15 /L), and hemolytic anemia (total bilirubin 4.6mg/dL, direct bilirubin 1.3 mg/dL, lactate dehydrogenase 488 U/L; negative result on direct and indirect Coombs tests and hemoglobinuria, cold-agglutinin reaction 256, but direct agglutination test was also negative, and haptoglobin was 8mg/dL), which was diagnosed as IgM warm autoimmune hemolytic anemia (AIHA), by a positive result on the IgM direct antiglobulin test. Bone marrow (BM) examination revealed myelofibrosis (MF)-1, hyperplastic BM with lymphocytic infiltration, without dysplasia in three lineages (Fig. 1c-f). The patient tested negative for JAK2V617F, CALR, and MPL mutation. Although the initial treatment for AIHA is steroid, as his AIHA type was atypical case, with a difficult diagnosis and delayed treatment, ruxolitinib 20 mg was started daily for MF, which normalized haptoglobin and reticulocyte levels without steroid treatment for AIHA (Fig. 1h). One year after ruxolitinib initiation, repeat BM examination revealed no fibrosis (Fig. 1g); CT showed improvement in splenomegaly (Fig. 1b). Ruxolitinib improved BM fibrosis, splenomegaly, and AIHA.

Conclusions

Autoimmune myelofibrosis (AIMF) is secondary MF associated with autoimmune diseases [1]. Thus, instead of Primary MF (PMF), the patient was retrospectively diagnosed with AIMF, supported by triple-negative and grade 1 MF, and lymphocytic infiltration of the BM, this is consistent with the characteristic

AIMF findings reported by Vergara-Lluri et al [2]. AIMF does not characteristically cause splenomegaly [1]. Spleen biopsy in this patient showed nonclonal lymphoid infiltrate, without evidence of extramedullary hematopoiesis, indicating AIHA-induced splenomegaly.

The treatment response of secondary MF is similar to that of PMF [3], whereas AIMF responds better than that of other secondary MF. In many cases, single-agent prednisolone can induce blood cell recovery; however, few cases show complete improvement of fibrosis [1].

There are few reports of MF with AIHA as the underlying disease. Fattizo et al. reported that 36% of AIHA had fibrosis [4]. IL-17 and IFN γ levels were correlated with increased LDH levels in AIHA, and predominantly higher transforming-growth factor (TGF)- β levels in patients with MF compared to those without fibrosis. They found that, in cases of AIHA-induced AIMF, TGF- β produced by lymphocytic BM infiltration induced BM fibrosis. AIHA with AIMF has poor response to PSL monotherapy, with patients requiring secondary therapy more frequently than those with MF0; with 70% of patients require rituximab, splenectomy, or other immunosuppressive agents, and have worse prognosis than AIHA alone [4]. JAK/STAT3 signaling is required for TGF- β -mediated transcriptional responses [5]. Ruxolitinib, a JAK/STAT signaling pathway inhibitor targeted drug, inhibits myeloproliferation, proinflammatory cytokine expression, and myeloid remodeling by the JAK-STAT pathway and other downstream pathways [6]. Here, ruxolitinib might improve cytokinemia, especially TGF- β , indicating effectiveness for both AIMF and AIHA. Rapid improvement of myelofibrosis by ruxolitinib monotherapy in AIMF patients or improvement of the autoimmune disease itself have not been reported previously. Thus, ruxolitinib is a potential therapeutic option for AIMF and AIHA in difficult-to-treat or when steroid therapy is a contraindicated.

Declarations

Compliance with ethical standards

Informed consent was obtained from the patient for the treatment.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

- i. Funding; Funding information is not available.
- ii. Conflicts of interest/Competing interests; The authors declare that they have no conflict of interest.
- iii. Ethics approval; The study was conducted in accordance with the Declaration of Helsinki.
- iv. Consent to participate (include appropriate statements); Written informed consent was obtained from from patient for publication of this case report and accompanying images.
- v. Consent for publication (include appropriate statements); Written informed consent was obtained from from patient for publication of this case report and accompanying images.
- vi. Availability of data and material (data transparency); Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

- vii. Code availability (software application or custom code); none.
- viii. Authors' contributions; SS was manuscript preparation and provided the pathology description. WK and YT read and approved the final manuscript.

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Figures

Figure 1

Before ruxolitinib treatment, abdominal computed tomography (CT) showed splenomegaly (a), and after 15 months of ruxolitinib treatment, splenomegaly has improved (b). Silver-staining of bone marrow biopsy showed MF-1 with a very loose network of reticulin fibers (c; ×200, d; ×400), with focal and interstitial lymphoid infiltrate, mainly of CD3 (+) small T-lymphocytes (e), and very few scattered CD79a (+) small B-lymphoid cells (f). After 15 months of continuous treatment with ruxolitinib, bone marrow

fibrosis had improved (g). Clinical course of the patient (h). We started ruxolitinib at 10mg daily and he had no problems, we upped to 20mg daily. Haptoglobin and reticulocyte levels also normalized with only ruxolitinib.