【 CASE REPORT 】

Recurrent Subcutaneous Sweet's Disease in a Myelofibrosis Patient Treated with Ruxolitinib before Allogeneic Stem Cell Transplantation

Teppei Sakoda[1], Yoko Kanamitsu[1], Yasuo Mori[1,2], Kensuke Sasaki[1], Etsuko Yonemitsu[3], Konosuke Nagae[3], Goichi Yoshimoto[1], Kenjiro Kamezaki[2], Koji Kato[1], Katsuto Takenaka[2], Toshihiro Miyamoto[1], Masutaka Furue[3], Hiromi Iwasaki[2] and Koichi Akashi[1,2]

Abstract:

Allogeneic hematopoietic stem cell transplantation (allo-SCT) has a curative potential for myelofibrosis (MF) patients; however, its association with a high therapy-related mortality (TRM) remains a big obstacle that needs to be overcome. Ruxolitinib (RUXO), a novel JAK1/2 inhibitor, can be used as a bridging therapy until allo-SCT can be performed to reduce TRM. We herein report a RUXO-treated MF patient who developed recurrent subcutaneous Sweet's disease (SSD) that was successfully treated by the administration of systemic glucocorticoids. We performed allo-SCT as previously scheduled, resulting in a good clinical course without deterioration of SSD. RUXO administration, as well as MF itself, might therefore sometimes cause this rare non-infectious event.

Key words: ruxolitinib, subcutaneous, Sweet's disease, myelofibrosis, stem cell transplantation

Introduction

Primary myelofibrosis (PMF) or post-essential thrombocythemia myelofibrosis (post-ET MF), classified as one of the classic BCR-ABL negative chronic myeloproliferative neoplasms (MPN), is a clonal hematological disorder characterized by bone marrow fibrosis, leukoerythroblastosis, splenomegaly, and constitutional symptoms (1). Genomic (e.g., *JAK2* (2), *MPL*, or *CALR* (3)) or epigenomic (e.g., *TET2* (4) or *EZH2* (5)) abnormalities, acquired at the hematopoietic stem cell level, are known to play a causative role through dysregulated Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signaling.

Allogeneic stem cell transplantation (allo-SCT) is the only curative option for patients with MF; however, there is a higher risk of graft failure or nonrelapse mortality (NRM) among patients with MF than for those with other diseases,

and this remains an issue that needs to be overcome (6).

Ruxolitinib (RUXO), a JAK1/2 inhibitor, mainly inhibits dysregulated JAK/STAT signaling, irrespective of the JAK2 mutational status. It could improve splenomegaly and constitutional symptoms by regulating proinflammatory cytokines and thereby have a positive impact on survival (7). As a result, the pretransplant administration of RUXO is greatly expected to reduce the spleen size, constitutional symptoms, and ultimately the risk of NRM during allo-SCT (8-10). In addition, RUXO before allo-SCT could potentially reduce the incidence or severity of graft-versus-host disease (GVHD) (10, 11), another main cause of NRM, by suppressing the function of dendritic cells (11, 12), T-cells (13), or NK-cells (14) including cytokine production. Its substantial immunosuppressive activity increases susceptibility to various types of microorganisms (e.g., Cryptococcus, Toxoplasma, or Mycobacterium tuberculosis) (15-17). In addition, a MF case which developed acute neutrophilic der-

[1]Medicine and Biosystemic Science, Kyushu University Graduate School of Medical Sciences, Japan, [2]Center for Cellular and Molecular Medicine, Kyushu University Hospital, Japan and [3]Department of Dermatology, Kyushu University Graduate School of Medical Sciences, Japan
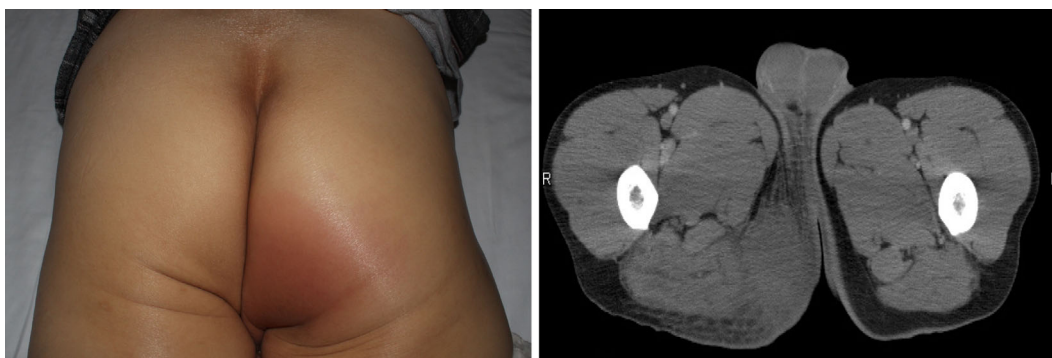
Figure 1. Macroscopic (left) and CT (right) findings of the erythematous plaque which developed in the patient's right buttock.

matosis (Sweet's disease) after stopping RUXO treatment has been recently reported (18).

We have also experienced a MF case with subcutaneous Sweet's disease (SSD), a variant type of Sweet's disease. It occurred repeatedly during RUXO administration and after cessation of the drug, however, it could be well controlled by systemic prednisolone (PSL) in the peritransplant period.

Case Report

A 59-year-old man with a 5-year history of post-ET MF was referred to our hospital for allo-SCT. On admission, he complained weight loss (3 kg in a month) and physical examination revealed hepatosplenomegaly with tenderness. Ultrasonography revealed a spleen index (SI) of 129.6. A complete blood count showed anemia [hemoglobin (Hb) 7.0 g/dL] that required regular blood transfusion, mild thrombocytopenia (platelets 133×10^9/L), and leukoerythroblastosis (blast, 1.5%; promyelocyte, 0.5%; myelocyte, 24.5%; and nucleated red blood cell, 1.5%/100 white blood cells). Coagulation and serum chemistry tests revealed normal results except for an elevated C-reactive protein level (1.71 mg/dL; normal range, <0.20 mg/dL). Bone marrow aspiration revealed a dry tap, and the biopsy specimen showed slight hypocellularity with diffuse fibrosis. A somatic mutation in the calreticulin gene, but not in the JAK2 gene, was detected using a direct sequencing method. Based on these findings, post-ET MF was diagnosed. The risk status was determined to be high-risk according to the International Prognostic Scoring System (IPSS) (19) and dynamic IPSS plus (20), although these systems might not be suitable for risk stratification among patients with post-ET MF (21). The MPN Symptom Assessment Form total symptom score (MPN-SAF TSS), that reflected severity of cytokine-mediated constitutional symptoms (22), was 22.

30 mg/day of RUXO was initiated to manage his splenomegaly/hypersplenism and subsequent progressive anemia/thrombocytopenia in order to reduce the risk of NRM at allo-SCT. At 7 weeks after RUXO initiation with an excellent response (Hb, 11.4 g/dL without blood transfusion; SI, 101.2 with no tenderness; MPN-SAF TSS, 7), the

patient developed a painful erythematous plaque on his right buttock (Fig. 1) with a high fever. A potent susceptibility to infection by RUXO (15-18, 23), and an operative history for internal hemorrhoids led us to initiate an empirical therapy with meropenem and daptomycin. On the next day, perineal and scrotal swelling emerged, and a CT scan demonstrated a soft tissue shadow with an indistinct boundary which spread from his right buttock to the perineal area (Fig. 1). These findings did not contradict those of necrotizing fasciitis (Frounier gangrene), and emergent surgical treatment was necessary. Unexpectedly, neither any remarkable debris nor necrotizing fascia was detected. A pathological examination of a punch biopsy and excision specimens revealed a dense neutrophilic infiltration predominantly in the lobules of the subcutaneous adipose tissue rather than in the dermis without vasculitis or necrosis (Fig. 2). Gram, Periodic acid-Schiff, and Grocott stains were negative for microorganisms, as were tissue and blood cultures for bacteria and fungi. Nevertheless, infectious panniculitis caused by undetected pathogens was most plausible at that moment. Combination therapy using meropenem and daptomycin continued; RUXO treatment was tapered down but not stopped to minimize the risk of its withdrawal symptoms (24). His general and focal condition gradually improved; however, on day 16, a similar painful erythematous lesion developed on the other side of the buttock, even though antibiotics were being administered. Various examinations indicated similar results. Given the clinical and pathological findings, the patient was diagnosed with SSD that may have been related to RUXO. RUXO was withheld together with 30 mg (0.5 mg/kg) of PSL; the skin lesion and fever both dramatically resolved. PSL could be tapered down to 5 mg without any recurrence of clinical symptoms. However, 7 weeks after the discontinuation of RUXO, when PSL was further tapered down to 2.5 mg, the erythematous plaque recurred; this time it appeared on the left forearm. His Hb level, SI, and MPN-SAF TSS were 11.7 g/dL, 107.5, and 11, respectively. Neither a deterioration of MF symptoms nor leukemic transformation was evident at that point. This new lesion, became exacerbated on day -23 of his scheduled allo-SCT, was also sensitive to PSL treatment. The patient then received a reduced-
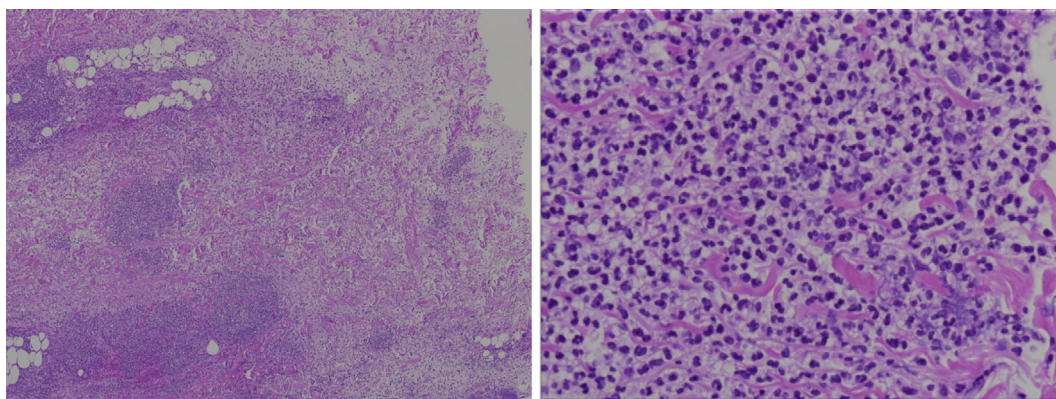
Figure 2. Pathologic examination revealed neutrophilic panniculitis without vasculitis. Original magnification was ×100 (left) and ×400 (right).

intensity conditioning regimen consisting of fludarabine (30 mg/sqm on days -8 to -3), busulfan (3.2 mg/kg on days -6 and -5), and total body irradiation (2 Gy in a single fraction on day -2) followed by matched unrelated bone marrow transplantation. The number of infused nucleated cells was $2.43×10^8$/kg. GVHD prophylaxis consisted of intravenous tacrolimus and short-term methotrexate. PSL used for SSD treatment, was gradually tapered off on day 49 and it positively contributed to GVHD prophylaxis. Granulocyte colony-stimulating factor (G-CSF) to accelerate neutrophil recovery was administered intravenously. A neutrophil count of $>0.5×10^9$/L was achieved on day 22, while transfusions of red cell concentrates and platelet concentrates were required on day 63 and day 43, respectively. Complete donor chimerism was observed in a blood sample on day 28 and in a bone marrow sample on day 53, indicating an improvement of the bone marrow environment; the bone marrow was still dry tap at that point. Neither engraftment syndrome nor acute GVHD was observed. No exacerbation of SSD was observed and cytomegalovirus antigenemia was always negative. The patient was discharged on day 64 with an excellent performance status.

Discussion

We herein report the case of a patient with post-ET MF who had recurrent SSD after RUXO initiation as a bridge therapy to allo-SCT. To the best of our knowledge, this is the second case of Sweet's disease/SSD after RUXO treatment described in the literature. Sweet's disease, originally reported by Robert Douglas Sweet in 1964, is clinically characterized by acute fever, leukocytosis, and painful erythematous plaques that mostly involve the extremities or head and neck, and histologically shows a dermal neutrophilic infiltrate without leukocytoclastic vasculitis. SSD is regarded as a subtype of Sweet's disease in which plaques or nodules with neutrophil infiltration are either localized within only the subcutaneous adipose tissue or involve both the dermis and the subcutaneous fat (25). Sweet's disease/SSD is frequently idiopathic: however, in a minority of

cases a possible etiologic association can be exhibited with infections, autoimmune disorders, myeloid malignancies, or medications.

A previous report (26) reviewed 15 cases of SSD developed among patients with myeloid disorders [myelodysplastic syndrome, n=8; acute myelogenous leukemia (AML), n=7]; however, no case of MPN was observed in the report. Another report (27) identified 21 cases of Sweet's disease, among 2178 AML cases that were closely related to AML with myelodysplasia-related features or mutated FMS-related tyrosine kinase-3 gene but not related to AML which developed from MPN. On the other hand, there are some case reports of Sweet's disease developed in MF patients (28, 29). The possibility that SSD was caused by underlying disease itself could not be ruled out in the present case, although RUXO improved the patient's clinical status (MPN-SAF TSS; 22 at pre-treatment, 7 at SSD onset, 11 at SSD recurrence).

The pathogenesis of Sweet's disease/SSD is still not clearly understood. However, altered immunologic reactivity, potentially involving cytokines is thought to be related. In fact, some drugs, including recombinant G-CSF (30), tyrosine kinase inhibitors (31, 32), or hypomethylating agents (33), could affect the cytokine levels and cause the Sweet's disease/SSD.

The JAK signaling pathway is indispensable for both cytokine production and its function; thus, we speculate that JAK1/2 inhibition could cause a dynamic change in the intricate cytokine network, although we could not completely elucidate its influence. Decreased MPN-SAF TSS (22 to 7) suggested an efficient inhibition of cytokine production. However, interleukin (IL)-1/IL-1R signal is transduced via the MyD88 pathway (34) independent of the JAK/STAT pathway; IL-1β promotes neutrophil survival and chemotaxis, and it presumably plays a causative role in Sweet's disease (35, 36). Less affected IL-1 signaling under RUXO administration might account for the first or second episodes. In contrast, the third episode might represent a focal sign of cytokine-rebound phenomena reported as the RUXO discontinuation syndrome (24), in which pro-inflammatory

cytokines, including IL-17, could be involved; indeed, MPN-SAF TSS was up to 11. A reported MF case with Sweet's disease developed 2 weeks after stopping RUXO due to loss of response (18); The Sweet's disease observed in the published case is mainly caused by the underlying MF, however dynamic change in the cytokine network after RUXO discontinuation might also have affected the patient's condition.

Another potent target of SSD is the RAS/RAF/MAPK pathway that exists downstream of JAK2. A BRAF inhibitor, vemurafenib, used against malignant melanoma has also been reported to cause this complication (37, 38).

Consistent with previous reports of other drug- or myeloid malignancy-induced Sweet's disease/SSD (26, 30-33, 37, 38), SSD developed in this case which was also found to be sensitive to PSL treatment. We could also manage this complication during the allo-SCT period. Continuous PSL treatment with gradual tapering down brought no recurrence of SSD even around the donor cells that were engrafted with G-CSF administration. Neither GVHD nor any severe infectious complications were observed.

In conclusion, we experienced recurrent SSD in a post-ET MF patient treated with RUXO before allo-SCT. Because the administration of RUXO before allo-SCT is expected to increase, hematologists should pay more attention to this rare non-infectious complication, which might be associated with the initiation/cessation of RUXO.

The authors state that they have no Conflict of Interest (COI).

References

1. Tefferi A, Thiele J, Orazi A, et al. Proposals and rationale for revision of the World Health Organization diagnostic criteria for polycythemia vera, essential thrombocythemia, and primary myelofibrosis: recommendations from an ad hoc international expert panel. Blood 110: 1092-1097, 2007.
2. Kralovics R, Passamonti F, Buser AS, et al. A gain-of-function mutation of JAK2 in myeloproliferative disorders. N Engl J Med 352: 1779-1790, 2005.
3. Nangalia J, Massie CE, Baxter EJ, et al. Somatic CALR mutations in myeloproliferative neoplasms with nonmutated JAK2. N Engl J Med 369: 2391-2405, 2013.
4. Tefferi A. Novel mutations and their functional and clinical relevance in myeloproliferative neoplasms: JAK2, MPL, TET2, ASXL 1, CBL, IDH and IKZF1. Leukemia 24: 1128-1138, 2010.
5. Ernst T, Chase AJ, Score J, et al. Inactivating mutations of the histone methyltransferase gene EZH2 in myeloid disorders. Nat Genet 42: 722-726, 2010.
6. Gupta V, Hari P, Hoffman R. Allogeneic hematopoietic cell transplantation for myelofibrosis in the era of JAK inhibitors. Blood 120: 1367-1379, 2012.
7. Verstovsek S, Mesa RA, Gotlib J, et al. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. N Engl J Med 366: 799-807, 2012.
8. Stübig T, Alchalby H, Ditschkowski M, et al. JAK inhibition with ruxolitinib as pretreatment for allogeneic stem cell transplantation in primary or post-ET/PV myelofibrosis. Leukemia 28: 1736-1738.
9. Shanavas M, Messner HA, Atenafu EG, et al. Allogeneic hematopoietic cell transplantation for myelofibrosis using fludarabine-, intravenous busulfan- and low-dose TBI-based conditioning. Bone Marrow Transplant 49: 1162-1169, 2014.
10. Jaekel N, Behre G, Behning A, et al. Allogeneic hematopoietic cell transplantation for myelofibrosis in patients pretreated with the JAK1 and JAK2 inhibitor ruxolitinib. Bone Marrow Transplant 49: 179-184, 2014.
11. Spoeri S, Mathew NR, Bscheider M, et al. Activity of therapeutic JAK 1/2 blockade in graft-versus-host disease. Blood 123: 3832-3842, 2014.
12. Heine A, Held SA, Daecke SN, et al. The JAK-inhibitor ruxolitinib impairs dendritic cell function in vitro and in vivo. Blood 122: 1192-1202, 2013.
13. Yajnanarayana SP, Stübig T, Cornez I, et al. JAK1/2 inhibition impairs T cell function in vitro and in patients with myeloproliferative neoplasms. Br J Haematol 169: 824-833, 2015.
14. Schönberg K, Rudolph J, Vonnahme M, et al. JAK inhibition impairs NK cell function in myeloproliferative neoplasms. Cancer Res 75: 2187-2199, 2015.
15. Wysham NG, Sullivan DR, Allada G. An opportunistic infection associated with ruxolitinib, a novel janus kinase 1,2 inhibitor. Chest 143: 1478-1479, 2013.
16. Goldberg RA, Reichel E, Oshry LJ. Bilateral toxoplasmosis retinitis associated with ruxolitinib. N Engl J Med 369: 681-683, 2013.
17. Colomba C, Rubino R, Siracusa L, et al. Disseminated tuberculosis in a patient treated with a JAK2 selective inhibitor: a case report. BMC Res Notes 5: 552, 2012.
18. Chatterjee B, Rqieh U, Greaves P, Piras D, Firth J, Saja K. Sweet syndrome as terminal event in ruxolitinib-treated myelofibrosis. Br J Haematol 169: 307, 2015.
19. Cervantes F, Dupriez B, Pereira A, et al. New prognostic scoring system for primary myelofibrosis based on a study of the International Working Group for Myelofibrosis Research and Treatment. Blood 113: 2895-2901, 2009.
20. Gangat N, Caramazza D, Vaidya R, et al. DIPSS plus: a refined Dynamic International Prognostic Scoring System for primary myelofibrosis that incorporates prognostic information from karyotype, platelet count, and transfusion status. J Clin Oncol 29: 392-397, 2011.
21. Hernández-Boluda JC, Pereira A, Gómez M, et al. The International Prognostic Scoring System does not accurately discriminate different risk categories in patients with post-essential thrombocythemia and post-polycythemia vera myelofibrosis. Haematologica 99: e55-e57, 2014.
22. Emanuel RM, Dueck AC, Geyer HL, et al. Myeloproliferative neoplasm (MPN) symptom assessment form total symptom score: prospective international assessment of an abbreviated symptom burden scoring system among patients with MPNs. J Clin Oncol 30: 4098-4103, 2012.
23. Landman GW, Arend SM, van Dissel JT. Ruxolitinib can mask symptoms and signs of necrotizing fasciitis. J Infect 66: 296-297, 2013.
24. Tefferi A, Pardanani A. Serious adverse events during ruxolitinib treatment discontinuation in patients with myelofibrosis. Mayo Clin Proc 86: 1188-1191, 2011.
25. Cohen PR. Subcutaneous Sweet's syndrome: a variant of acute febrile neutrophilic dermatosis that is included in the histopathologic differential diagnosis of neutrophilic panniculitis. J Am Acad Dermatol 52: 927-928, 2005.
26. Chan MP, Duncan LM, Nazarian RM. Subcutaneous Sweet syn-

drome in the setting of myeloid disorders: a case series and review of the literature. J Am Acad Dermatol **68**: 1006-1015, 2013.

27. Kazmi SM, Pemmaraju N, Patel KP, et al. Characteristics of Sweet syndrome in patients with acute myeloid leukemia. Clin Lymphoma Myeloma Leuk **15**: 358-363, 2015.

28. Su WP, Alegre VA, White WL. Myelofibrosis discovered after diagnosis of Sweet's syndrome. Int J Dermatol **29**: 201-204, 1990.

29. Altomare G, Capella GL, Frigerio E. Sweet's syndrome in a patient with idiopathic myelofibrosis and thymoma-myasthenia gravis-immunodeficiency complex: efficacy of treatment with atretinate. Haematologica **81**: 54-58, 1996.

30. Bidyasar S, Montoya M, Suleman K, Markowitz AB. Sweet syndrome associated with granulocyte colony-stimulating factor. J Clin Oncol **26**: 4355-4356, 2008.

31. Assouline A, Laneuville P, Gambacorti-Passerini C. Panniculitis during dasatinib therapy for imatinib-resistant chronic myelogenous leukemia. N Engl J Med **354**: 2623-2624, 2006.

32. Zhang M, Hassan KM, Musiek A, Rosman IS. Ponatinib-induced neutrophilic panniculitis. J Cutan Pathol **41**: 597-601, 2014.

33. Kim IH, Youn JH, Shin SH, et al. Neutrophilic panniculitis following azacitidine treatment for myelodysplastic syndromes. Leuk Res **36**: e146-e148, 2012.

34. Burns K, Martinon F, Esslinger C, et al. MyD88, an adapter protein involved in interleukin-1 signaling. J Biol Chem **273**: 12203-12209, 1998.

35. Marzano AV, Fanoni D, Antiga E, et al. Expression of cytokines, chemokines and other effector molecules in two prototypic autoinflammatory skin diseases, pyoderma gangrenosum and Sweet's syndrome. Clin Exp Immunol **178**: 48-56, 2014.

36. Bourke JF, Jones JL, Fletcher A, Graham-Brown RA. An immunohistochemical study of the dermal infiltrate and epidermal staining for interleukin 1 in 12 cases of Sweet's syndrome. Br J Dermatol **134**: 705-709, 1996.

37. Zimmer L, Livingstone E, Hillen U, Dömkes S, Becker A, Schadendorf D. Panniculitis with arthralgia in patients with melanoma treated with selective BRAF inhibitors and its management. Arch Dermatol **148**: 357-361, 2012.

38. Kim GH, Levy A, Compoginis G. Neutrophilic panniculitis developing after treatment of metastatic melanoma with vemurafenib. J Cutan Pathol **40**: 667-669, 2013.