Case Report

Rapid Hepatomegaly From Ruxolitinib Discontinuation Syndrome

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Abstract

Introduction
Ruxolitinib (RUX) is a Food and Drug Administration-approved Janus Kinase (JAK) inhibitor shown to be effective in improving hypercatabolic symptoms and splenomegaly in patients with myelofibrosis (MF). RUX therapy provides symptomatic benefits for MF patients but is often discontinued for various reasons including worsening cytopenias. Ruxolitinib Discontinuation Syndrome (RDS) involves an acute cytokine-storm rebound phenomenon that can manifest as an acute relapse of symptoms, worsening splenomegaly, respiratory distress, systemic inflammatory response syndrome, or disseminated intravascular coagulopathy.

Case Presentation
We present the case of a patient with JAK2-positive post-polycythemia vera MF, whose RUX therapy was discontinued due to an active gastrointestinal (GI) bleed and worsening cytopenias. The patient had recently started azacitidine and was on the drug combination prior to hospitalization. The patient developed what appears to be the first case of acute onset accelerated massive hepatomegaly, a previously undescribed clinical manifestation of RDS.

Conclusion
Although rare, medical professionals should maintain a high suspicion of RDS in hospitalized patients following the discontinuation of RUX.

Keywords
ruxolitinib; Ruxolitinib Discontinuation Syndrome; RDS; myeloproliferative disorders; myelofibrosis; MF; hepatomegaly; gastrointestinal hemorrhage; polycythemia vera; extramedullary hematopoiesis; myeloproliferative neoplasms; Janus kinase inhibitor; drug therapy

Introduction
Myeloproliferative neoplasms classically include polycythemia vera, essential thrombocytopenia, primary myelofibrosis (MF), and chronic myeloid leukemia. These myeloproliferative neoplasms are characterized by unchecked proliferation of myeloid, erythroid, or megakaryocyte lineage components. JAK2V617 genetic mutations are found in all patients with primary polycythemia vera and approximately 50% of patients with either primary essential thrombocytopenia or primary MF.[1] Based on the type of myeloproliferative neoplasms, patients are at varied risk for hepatosplenomegaly, thrombosis, and conversion to MF or acute myeloid leukemia.

Our case report focuses on a patient with JAK2-positive post-polycythemia vera MF. Typical MF symptoms include constitutional symptoms secondary to cytokine-related hyper-catabolism, extramedullary hematopoiesis (EMH) with splenomegaly, portal hypertension with varices, abdominal discomfort, and early satiety. The only curative option for MF is an allogeneic hematopoietic stem cell transplant. Other available medical therapies do not halt disease progression, and current treatment

strategies have focused on drugs targeting specific symptomatology.[2]

Ruxolitinib (RUX) is an ATP mimetic JAK1/JAK2 inhibitor shown to be effective in improving hypercatabolic symptoms and splenomegaly in patients with MF and is currently Food and Drug Administration (FDA)-approved for patients with intermediate-risk or high-risk MF and a baseline platelet count of 50x10^3/uL or more.[3] Despite the symptomatic improvement in constitutional symptoms provided, RUX use is associated with critical adverse side effects, including moderate to severe thrombocytopenia and anemia.[4] Previous studies have thus documented a high discontinuation rate (40% of patients discontinue treatment within 3 years of therapy, 92% of them after a median of 9.2 months), primarily for loss of treatment benefit but also due to drug-associated adverse effects.[5] A handful of previous reports have also described a withdrawal syndrome termed Ruxolitinub Discontinuation Syndrome (RDS) in patients who have stopped treatment. RDS includes an acute relapse of symptoms, worsening splenomegaly, and life-threatening adverse events, including respiratory distress, systemic inflammatory response syndrome, and disseminated intravascular coagulation-like syndrome.[5-7] A situation similar to tumor-lysis syndrome also has been reported in the context of RDS.[8] These events have been attributed to an acute cytokine-storm rebound phenomenon, and the adverse events typically seem to resolve rapidly with RUX reintroduction.[7]

A recent multicenter study looked at 251 RUX-treated MF patients who discontinued RUX after a median time of 36.1 months. It documented RDS in 34 (13.5%) patients after a median time of 7 days (range 2-21).[7] They defined RDS as new symptoms occurring 21 days from RUX discontinuation and were interpreted by the treating hematologist to be attributed to RUX discontinuation. They characterized RDS as either mild (no interventions required), moderate (symptoms required medical interventions including restarting RUX, steroids, oral analgesics), or severe (intravenous [IV] medications, hospital admissions, splenectomy, or delaying of hematopoietic cell transplantation). They found mild RDS in 21 patients (61.8%), moderate RDS in 10 patients (29.4%), and severe RDS in 3 patients (8.82%). RDS therapies included corticosteroids, a trial with a non-JAK-inhibited (JAKi), or a RUX re-challenge. They concluded that there was no association between the RUX dose at the time of the discontinuation, tapering use, or clinical laboratory parameters. They found that RDS was significantly associated with the need for RUX re-challenge, with 8 of the 34 RDS patients (23.5%) eventually resuming RUX.[7]

We seek to expand on this rare but emerging and clinically significant RDS phenomenon by presenting a case report of a JAK2-positive post-polycythemia vera MF patient in whom RUX was discontinued. While hospitalized, the patient subsequently developed rapid severe RDS with accelerated hepatomegaly, a previously undescribed manifestation of RDS.

Case Presentation

We present the case of a White male patient above age 80 with JAK2-positive post-polycythemia vera MF. He was in the cellular phase of MF and was actively being treated with RUX 20 mg by mouth twice daily and had received treatment with cycle 1, day 1 (C1D1) of azacitidine 1 week prior to admission. He had been on RUX therapy for 18 months with no prior discontinuation. His baseline levels of white blood cells (WBCs), hemoglobin (Hgb), and platelets 1 week prior to hospitalization were 88.7x10^3/uL, 12.9g/dL, and 134x10^3/uL, respectively. He had no palpable hepatosplenomegaly, abdominal pain, or constitutional symptoms associated with MF such as fever, fatigue, night sweats, or weight loss prior to hospitalization.

He presented to our emergency department with an acute gastrointestinal (GI) bleed. Initial lab results at the time of presentation were WBC 90.0x10^3/uL, Hgb 10.1g/dL, and platelets 101x10^3/uL. A computed tomography (CT) scan of the abdomen and pelvis with IV contrast showed active bleeding but no abnormalities in the liver or spleen (**Figure 1**). His initial stabilization required a massive transfusion protocol, intubation, and emergent abdominal surgery. He subsequently underwent an exploratory laparotomy with partial gastrectomy and suture ligation of 2 Dieulafoy lesions. RUX was held given his acute GI bleed, worsening transfusion-dependent anemia, and thrombocytopenia now persistently less than 50x10^3/uL.

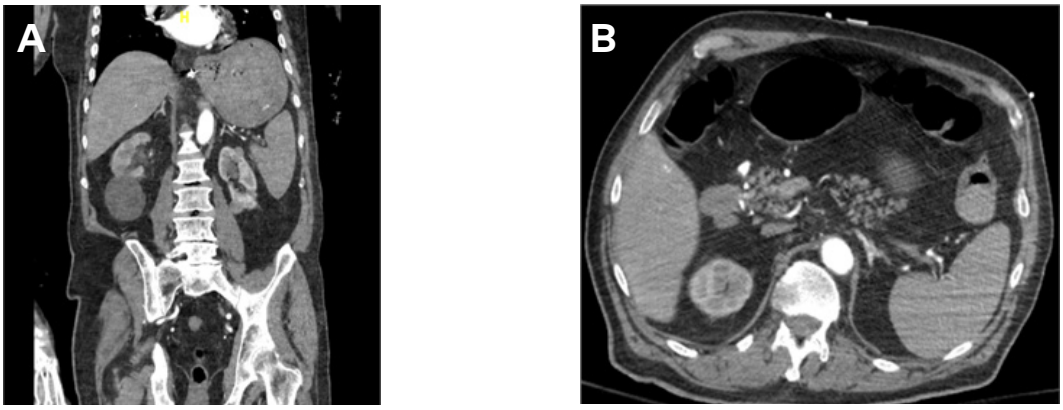

Figure 1. A CT of the abdomen and pelvis with IV contrast on admission (**A.** coronal and **B.** transverse) shows extravasation of contrast within the stomach, compatible with active bleeding, but no hepatomegaly or splenomegaly.

Despite receiving multiple transfusions of packed red blood cells, platelets, and fresh frozen plasma, he displayed worsening anemia and thrombocytopenia over the next several days that required additional transfusions. Lab work on the fifth day of hospitalization showed WBC 8.8x10^3/uL, Hgb 6.9g/dL, and platelets 27x10^3/uL. An esophagogastroduodenoscopy was performed on day 6 and showed no active bleeding. He developed a fever with a maximum temperature of 101.8° F, abdominal pain, and abdominal distention suspicious for palpable organomegaly. A repeat CT scan of the abdomen and pelvis with IV contrast on day 6 showed a new splenomegaly of 21.5 cm with a subcapsular hematoma and new hepatomegaly of 21.8 cm, **Figure 2**). Subsequent imaging, including a triple-phase helical abdominal CT with IV contrast and Doppler ultrasounds, revealed no evidence of splenic vein or portal vein thrombosis. A peripheral blood smear showed large numbers of nucleated red cells, indicating compensatory erythropoiesis in the setting of EMH and JAK2-positive post-polycythemia vera MF.

A presumptive diagnosis of RDS was made, and his RUX treatment was restarted at a lower dose of 15 mg daily. He was also started on high-dose corticosteroids. His fever and abdominal complaints rapidly resolved, and he was ultimately transferred to a neighboring tertiary care facility for closer evaluation and monitoring. At the neighboring facility, a decision was made to taper off RUX therapy over a period of 2 weeks by 5 mg twice daily with each taper. Once the taper was complete, the plan was to initiate treatment with the novel second-generation JAKi, pacritinib, as it reportedly has less of an effect on platelet count than RUX. Upon follow-up after discharge, he remained asymptomatic, and there was no palpable hepatosplenomegaly. Additionally, the patient's WBC, Hgb, and platelets appeared

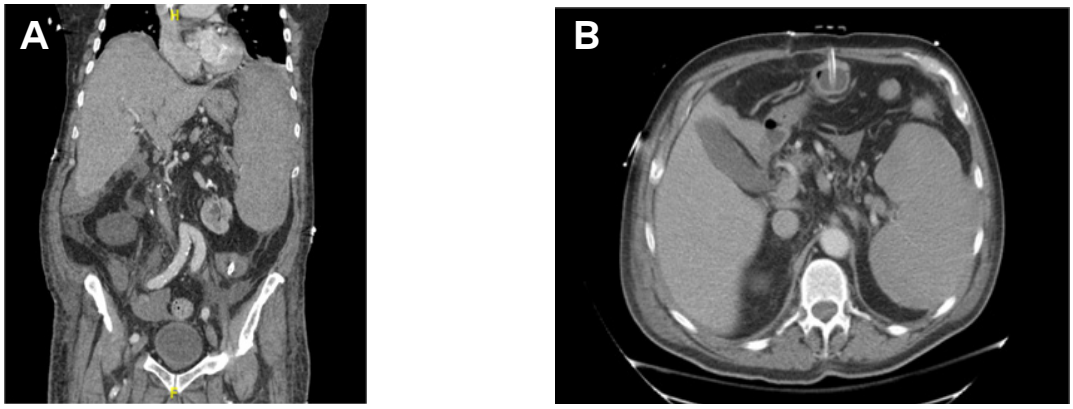

Figure 2. A CT of the abdomen and pelvis with IV contrast on hospital day 6 (**A.** coronal and **B.** transverse) now shows a new splenomegaly of 21.5 cm with a subcapsular hematoma of 11.3 x 1.8 cm and a new hepatomegaly of 21.8 cm.

to have returned to his baseline at 9.7x10^3/uL, 11.4g/dL, and 122x10^3/uL, respectively. He was continuing his taper off of RUX therapy with the continued plan to eventually start pacritinib therapy.

Discussion

This patient's acute GI bleed was secondary to vascular malformation, likely exacerbated by worsening thrombocytopenia and anemia from RUX and azacitidine treatment. Considering the patient required emergent surgical intervention and a massive transfusion protocol for stabilization in the setting of platelet counts consistently below 50x10^3/uL, RUX could not be restarted. The decision was made to discuss restarting the treatment outpatient.

RDS is then seen in this patient, evidenced by worsening cytopenia despite ongoing transfusions, the development of rebound cytokine-storm-related constitutional symptoms including fever with a systemic inflammatory response syndrome-like response, and the acute onset of new accelerated massive hepatosplenomegaly with abdominal pain. The time of onset of RDS in this patient was 5-6 days from discontinuation of his RUX. That is when his cytopenia worsened, and he first became febrile and started to develop abdominal pain secondary to his new hepatosplenomegaly. This time of onset supports the 1 to 21-day timeline of RDS development previously described, and he met the criteria for severe RDS, given the need for ongoing hospitalization and IV medications.[7]

While most of our patient's RDS symptoms have been well described in previous reports, we present a novel finding of acute onset rapid hepatomegaly as a possible additional feature of RDS, which has yet to be described. Per our literature review at the time of writing, this appears to be the first documented case of accelerated hepatomegaly secondary to RDS.

Up to 65% of MF patients have hepatomegaly.[9] MF patients are at a higher risk for developing portal hypertension and splenic or portal vein thromboses.[10] Our patient did not have hepatosplenomegaly at baseline, nor did he have any identifiable portal hypertension, varices, or thromboses of the hepatic or splenic-portal veins on esophagogastroduodenoscopy or imaging. Additionally, hepatomegaly in these instances is typically chronic and would not usually present with such rapid onset as was seen in our patient. Additionally, it should not rapidly improve with the resumption of RUX therapy, suggesting that the acute hepatosplenomegaly documented in our patient likely has another cause.

One hypothesis for our patient's acute onset hepatomegaly could be a potential rebound EMH phenomenon in the setting of his RUX discontinuation. EMH in MF chiefly takes place in the spleen and liver.[11] While the spleen is thought to be the leading site of EMH, the liver has also been implicated in various disease states, such as MF. In certain pathological states such as MF, hematopoietic stem cells and hematopoietic progenitor cells, particularly MF-stem cells, can be released in large numbers into the bloodstream. Once in the bloodstream, they migrate to other organs such as the liver, causing hepatic myeloid metaplasia. Under these conditions, the liver works to compensate for the bone marrow's deficiency and, together with the spleen, attempts to remedy the lack of functional blood cells.[11] MF CD34+ cells have been theorized to play a role in this process.[12]

RUX has previously been shown to improve EMH, specifically pulmonary EMH.[13] Additionally, the pivotal phase III Controlled Myelofibrosis Study with Oral JAK Inhibitor Treatment I (COMFORT-1) showed RUX to significantly reduce splenomegaly and symptoms in patients with MF.[14] One COMFORT-I post hoc analysis suggested that RUX is effective in providing a rapid and sustained reduction in MF-related hepatomegaly.[15]

It is therefore reasonable to conclude that the discontinuation of our patient's RUX caused a rebound in the activation of cytokines and chemokines. This caused accelerated EMH which ultimately resulted in the observed acute hepatosplenomegaly, a previously undescribed manifestation of RDS. This hypothesis is further supported by the observed rapid resolution of symptoms and clinical improvement in the patient once the RUX was restarted.

A limitation of this case report is that no additional radiographic imaging was performed to document the resolution of his hepatosplenomegaly. However, the liver and spleen were no longer palpable upon physical exam, and the patient reported resolution of abdominal discomfort and early satiety. These findings all suggest improvement of an acute hepatosplenomegaly.

It is unclear if some of our patient's symptoms related to his RUX discontinuation, including his rapid hepatosplenomegaly, could have been mitigated with a personalized tapering RUX schedule or further augmentation with a more robust steroid regimen. Although various RUX tapering schedules and concurrent steroid regimens have been utilized in some studies[7], there are no formal guidelines for RUX discontinuation to limit or avoid RDS in patients who require discontinuation of their RUX therapy.

Of interest, a new phase III randomized international multicenter study, the PERSIST-2 study, recently compared the efficacy and safety of pacritinib, a novel JAK2/tyrosine kinase 3 inhibitor with negligible activity against JAK1, with that of the best available therapy, including RUX in patients with MF and thrombocytopenia. The study involved patients with a platelet count of $100x10^3$/uL.[16] The study concluded that pacritinib was more effective than the best available therapy for reducing splenomegaly and symptoms.[16] Since our encounter with this patient, pacritinib has been approved by the FDA for treating patients with intermediate or high-risk MF with a platelet count of less than $50x10^3$/uL[17], assisting in addressing the needs of patients with cytopenic MF. It remains to be seen if this novel JAK2 inhibitor will also carry the risk of a discontinuation-like syndrome of its own. As pacritinib possesses only negligible activity against JAK1, it may possibly display less of a cytokine-storm rebound phenomenon and may potentially be more tolerable to discontinuation than RUX.

Conclusion

We have presented a novel case of acute onset accelerated massive hepatomegaly in the setting of RUX discontinuation, which appears to be a previously undescribed clinical manifestation of RDS. Additional research is needed to further elucidate the potential mechanism for rapid hepatomegaly in RDS patients, to determine formal treatment guidelines for tapering RUX therapy with or without the addition of a steroid regimen to mitigate RDS, as well as to shed light on the role of the emerging alternate MF therapy pacritinib. Although rare, medical professionals should maintain a high suspicion of RDS in hospitalized patients following the discontinuation of RUX.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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