Severe ARDS due to Ruxolitinib discontinuation syndrome: case presentation and literature review

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ABSTRACT

Objective: Discontinuation of Ruxolitinib (RUX), a JAK1/JAK2 inhibitor, can induce symptom-relapse and even life-threatening adverse events. Due to increasing use of RUX, this so-called RUX discontinuation syndrome (RDS) is becoming more prevalent. To create better awareness for this potentially fatal syndrome, we present a case of an adult male who developed a fatal RDS.

Results: Our case presented with acute respiratory failure and a shock-like syndrome, with the need for mechanical ventilation, venovenous-extracorporeal membrane oxygenation (ECMO) and vasopressors. Respiratory symptoms quickly improved after initiation of corticosteroids, but disease course was complicated with a spontaneous spleen rupture leading to hemorrhagic shock and eventually death.

Conclusion: This case report is the first case of severe RDS necessitating vv-ECMO and complicated with spleen rupture. Clinicians should be aware of this potentially lethal syndrome as it can present acutely but be effectively treated with corticosteroids and/or restarting JAK-inhibitors.

1. Introduction

Ruxolitinib (RUX) is a selective Janus kinase (JAK) 1 and 2 inhibitor, approved for the treatment of myeloproliferative neoplasms (MPN). Janus kinases are important tyrosine kinases that facilitate cell signaling. JAK1 provides cell signaling for receptors that are activated by different interleukins and interferon, and JAK2 for receptors that are activated by hormone-like cytokines such as erythropoietin and thrombopoietin [1]. By inhibiting cytokine signaling, JAK inhibitors decrease inflammatory and hematopoietic reactions, leading to symptomatic reduction in myelofibrosis [2, 3, 4, 5]. After sudden cessation of JAK-inhibitor therapy, a withdrawal syndrome can occur, presenting with symptoms of a cytokine storm, such as acute respiratory distress syndrome (ARDS), septic-like shock and disseminated intravascular coagulation (DIC)-like syndrome [6, 7, 8]. Although rare, more cases are being reported due to the growing use of RUX [6, 7, 8]. In a study of Palandri et al. 13.5% of patients presented RDS after RUX discontinuation, including 1.2% with severe RDS [6]. We present a fatal case of Ruxolitinib discontinuation syndrome (RDS) with severe ARDS, requiring venovenous (vv)-ECMO, and provide a review of the literature.

2. Case presentation

A 56-year-old man with primary myelofibrosis was transferred to our university tertiary care ICU after retrieval on mobile VV-ECMO for severe acute respiratory failure. The patient had a history of chronic back pain with daily opioid use and paroxysmal atrial fibrillation. He was diagnosed with V617F JAK2 positive primary myelofibrosis in 2014. Treatment was initiated with hydroxyurea in 2018 because of increasing anaemia, leukocytosis and splenomegaly. Because of peripheral blastosis, splenomegaly and constitutional symptoms, he started in 2019 a combination therapy with ruxolitinib (JAKAVI®), a JAK1/JAK2-inhibitor) and a BET (Bromodomain and Extra-Terminal motif)-inhibitor. The patient was offered allogeneic bone marrow transplantation but preferred the combination therapy.

After an initially very good clinical response, in early 2021, disease progression was noted with progressive thrombocytopenia and increase
in spleen volume (estimated volume of 3382 ml on CT scan and estimated 13 cm under costal margin on palpation; threshold for splenomegaly is 450 ml).

Because of thrombocytopenia as dose limiting toxicity (DLT) and progressive disease, his treatment with RUX (of 10 mg 2x/d) and the BET-inhibitor was temporarily stopped.

One week later, the patient presented to his local hospital with acute hypoxemic respiratory failure and hypotension. The patient was extremely dyspnoeic and in distress but had no fever and denied any other symptoms. An arterial blood gas showed respiratory acidosis with a pH of 7.2, pCO2 of 59 mmHg and pO2 of 53 mmHg at room air. He was urgently intubated and started on intravenous antibiotics, norepinephrine and hydrocortisone for presumed septic shock. CT scanning without contrast, showed diffuse bilateral patchy infiltrates sparing the peripheral lung zones and no pulmonary embolism as shown in Figure 1.

Because of refractory hypoxemia and hypercapnia, the patient was placed on VV-ECMO by our ECMO retrieval team and transferred to our hospital.

Laboratory results at admission in our hospital showed a mild macrocytic anaemia of 11.4 g/dl, leukocytosis of 25.68 l. High-sensitive CRP of 39 mg/L, ESR of 91 mm/hour, procalcitonin (PCT) of 8.1 ng/ml were normal. Other lab results were unremarkable. BUN reactive protein was elevated at 53.7 mg/l (previous lab values normal), troponin I was slightly elevated at 68.7 pg/ml (normal <40 pg/ml). C-reactive protein was elevated at 53.7 mg/l (previous lab values normal), and D-dimers were negative. Other lab results were unremarkable. BUN and creatinine were normal; ANCA, ANA and anti-glomerular basement membrane antibodies were also negative. Bronchoscopy at admission was unrevealing. Bronchoalveolar lavage was negative for SARS-CoV-2, and viral respiratory panel and cultures also proved negative.

Echocardiography (on ECMO) showed a dilated right ventricle, with prominent D-shaping and severe pulmonary hypertension with an estimated systolic PAP of 80 mmHg + CVD (19 mmHg). In order to support the right ventricle, inhaled nitric oxide and intravenous milrinone were started. Follow-up echocardiography the next day, showed marked improvement in cardiac function with reduction of right ventricle size and disappearance of abnormal septal motion.

During the first days, we saw a rapid improvement in lung mechanics, radiological findings, ventilation and oxygenation as well as shock state. We were able to gradually wean the patient off VV-ECMO. At day 5 of ICU admission, sweep gas flow on ECMO was stopped and decannulation planned later that day.

Unexpectedly, the patient developed a haemorrhagic shock due to a spontaneous splenic rupture. Despite selective embolization of a branch of the splenic artery, the patient deteriorated further, requiring massive transfusion and high doses of norepinephrine and adrenaline. He developed a severe abdominal compartment syndrome, for which an urgent laparotomy with splenectomy was performed. Perioperatively, about 5 L of blood were evacuated from his abdomen, resulting in hemodynamic improvement with concomitant transfusion.

After his surgery we decided to restart RUX at a reduced dose of 2 x 5 mg/d. In the following days he developed a progressive hyperleukocytosis (>100 x 109 cells/L), with a risk of hyperviscosity syndrome for which additional cytoreductive therapy was started with hydroxyurea. Although our patient initially stabilized after splenectomy, we had to start renal replacement therapy and he continued to require daily transfusions. After his splenectomy he had 9 relook surgeries for haemostasis due to continuous blood loss, despite adequate coagulation tests, including visco-elastic testing. During his hospitalization of about 7 weeks, he received daily transfusion of platelets, in total 95 pools of platelets, 85 units of RBC and 30 units of fresh frozen plasma. His condition was further complicated with invasive pulmonary aspergillosis in week 6. His underlying immunocompromised state, multiple transfusions, long ICU stay and a staphylococcal toxic shock syndrome in week 7 lead to multiple organ failure and death due to refractory septic shock. An overlook of the clinical sequence is presented in Table 1.

3. Discussion and review of the literature

We describe a fatal case of ARDS and septic-like shock, further complicated with splenic rupture and haemorrhagic shock, likely caused by a rebound cytokine storm after abrupt cessation of JAK-inhibitor therapy, the so-called Ruxolitinib discontinuation syndrome (RDS). Several case series have been published with respiratory failure, septic-like shock and DIC after withdrawal of RUX therapy [6, 7, 8]. In the present case, severe clinical symptoms started 4 days after stopping RUX due to progressive thrombocytopenia. Treatment with hydrocortisone, started for presumed refractory septic shock, could explain why he improved initially, as corticosteroid administration is part of the treatment for RDS.

Ruxolitinib is a JAK1 and JAK2 inhibitor. The Janus kinases (JAK) are cytoplasmic protein tyrosine kinases that are essential for signal transduction for interleukin (IL)-2, IL-4, IL-7, IL-9, IL-15, and IL-21, especially through JAK-STAT (signal transducer and activator of transcription) signalling. STAT activation induces cytokines and growth factors, that play a role in haematopoiesis, immunity, inflammation, tissue repair, and apoptosis. Most immune responses are dependent on STAT.

Myeloproliferative neoplasms (MPN) are hematopoietic stem cell disorders with mutations that continuously stimulate JAK-2 and consequently the intracellular JAK-STAT pathway. The dysregulated JAK signalling leads to proliferation of hematopoietic cells and a chronic inflammatory state caused by the overproduction of cytokines. Primary myelofibrosis (PMF) is the least common and most aggressive MPN. PMF usually presents with symptomatic splenomegaly, debilitating systemic symptoms and cytopenia in differing degrees, and is associated with reduced life expectancy. Treatment options for myelofibrosis include

Table 1. Clinical sequence.

| Year | Event |
|------|-------|
| 2014 | Diagnosis of PMF |
| 2018 | Start hydroxyurea |
| 2019 | Start Rux + BET-inhibitor |
| 2021 | Stop Rux + BET-inhibitor |
| week 1 | ARDS, shock, vv-ECMO, splenectomy |
| week 2-6 | Nine relook surgeries |
| week 7 | STS, MOF, death |

PMF = primary myelofibrosis, Rux = ruxolitinib, BET = Bromodomain and Extra-Terminal Motif

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stem cell transplantation, JAK inhibitors and supportive therapy (including hydroxyurea) [9].

Ruxolitinib is a fairly new treatment for PMF. It inhibits the JAK-STAT pathway that is upregulated in myelofibrosis. Long-term follow-up studies of its safety and efficacy confirm that it provides rapid and durable improvements in symptoms, splenomegaly, and quality of life, and even survival [3, 5]. The response to RUX does not seem to be determined by the underlying driver mutation, but is affected by non-driver mutations [2, 3, 4]. Ruxolitinib might also reverse or significantly delay bone marrow fibrosis [6] but this finding is rare and is considered as anecdotal.

The effect on constitutional symptoms and splenomegaly is excellent in most patients, but treatment discontinuation rate is also high because of loss of treatment benefit or adverse effects. A retrospective analysis of 20 European haematology centres and 524 patients, showed a discontinuation rate of 40% after 3 years [10]. Because the JAK/STAT pathway has a vital role in erythropoiesis and thrombopoiesis, RUX can cause dose-related anaemia and thrombocytopenia [11]. Thrombocytopenia is usually the dose limiting toxicity.

Because of progressive myelofibrosis our patient was started on RUX and a BET-inhibitor, with good clinical response for about 18 months. His treatment was eventually interrupted because of progressive thrombocytopenia. Thrombocytopenia is also related to poorer outcomes. High rates of thrombocytopenia within the initial weeks of RUX therapy may lead to dose reduction or even discontinuation of treatment, entailing a risk of rapid recurrence of splenomegaly and systemic symptoms [4, 17].

A recent review by Palandri et al. of 251 patients who discontinued RUX therapy, showed RDS in 34 patients (13.5%). Symptoms were mild in 21 patients (61.8%), with symptomatic spleen enlargement and constitutional symptoms. Symptoms were moderate in 10 out of 34 (29.4%), requiring treatment with corticosteroids or restarting JAK-inhibitors. Three patients (8.8%; <1% of patients who stopped RUX therapy) presented with a severe discontinuation syndrome (spleen rupture, ARDS or septic like shock), which required ICU admission. In their review, Palandri also suggests that due to the different approaches among centres there is a need for more uniform therapeutic strategies for discontinuing RUX therapy [6].

Ruxolitinib discontinuation syndrome can occur as early as 48 h up to 3 weeks after discontinuation of RUX and even after gradual tapering of the dose [8]. It is still a diagnosis by exclusion, seeing there is no specific marker indicating withdrawal syndrome. Symptoms of RDS are probably caused by a rebound “cytokine storm” [6, 7, 8]. An important risk factor to developing RDS seems to be disease activity. Patients with worse splenomegaly (>10 cm below costal margin) and platelet count <100 × 109/l, had an increased risk at RDS with therapy interruption in multivariate analysis [6]. Although the risk of RDS seems to be related to symptom severity [10], disease progression is also often the reason for RUX discontinuation. Therefore, this relationship may not be causal.

Respiratory failure with bilateral ground glass opacities on CT seems to be a common symptom of severe withdrawal. A septic shock-like presentation has also been described [7, 8]. In most cases RUX was restarted, together with corticosteroids, after which the patients gradually improved.

Our patient had stopped treatment for 4 days before presenting with respiratory failure. He was in shock at presentation requiring vasopressors during the first days of admission. His respiratory state and hemodynamic status gradually improved during mechanical ventilation and vv-ECMO. Treatment with corticosteroids probably added to a significant improvement during the first few days. After his splenectomy RUX was also restarted at a reduced dose of 10 mg/day. Although there are no clear guidelines for stopping RUX treatment, we would advise to always taper the dose when stopping treatment, and also considering a low dose of corticosteroids for a short period.

As far as we know, this is the first case with such a dramatic presentation, requiring early vv-ECMO.

Survival after RUX discontinuation overall seems poor. Newberry et al. showed in his retrospective study a median survival of 14 months after discontinuation [12]. RUX was often stopped due to therapy failure and disease progression, so we cannot conclude RUX discontinuation itself leads to a worse prognosis. Low platelets at the start and end of therapy were also associated with worse prognosis.

A recent observational multicenter retrospective study, compared mortality rate due to covid-19 infection of MPN-patients with a general population [13]. No increased mortality was seen in patients with essential thrombocytopenia, polycythemia vera, or pre-fibrotic myelofibrosis. In patients with symptomatic myelofibrosis, mortality was significantly higher than the general population and reached up to 48%. Interestingly most of the increased mortality seemed related to the discontinuation of RUX. With a survival rate at 60 days of 68% if ruxolitinib was continued, compared to 11% if it was discontinued. A logistic multivariable model showed significant increased mortality after RUX discontinuation (OR 8.4 with p 0.04). This was a retrospective study, and patients where RUX therapy was stopped may have had a worse prognosis, regardless of RUX therapy. Nevertheless, this study seems to suggest that discontinuing RUX during an acute infection will lead to worse outcomes. Possibly due to the sudden increase in cytokines and inflammation.

Our case was also complicated by a splenic rupture after initial clinical improvement, probably also caused by the RDS with increased splenic sequestration.

Hematologic malignancies, including myelofibrosis can rarely lead to a spontaneous splenic rupture [14, 15, 16]. Cases have even been described where the initial presentation of myelofibrosis was abdominal distention due to splenomegaly with subcapsular hematoma [16].

Angiographic embolization was attempted first in our patient. Due to the substantial risk of post-splenectomy infections and effects on the underlying disease (with extra-medullary haematopoiesis in other places), non-operative management with sparing of the spleen is preferred in hemodynamically stable patients [17]. Unfortunately, our patient developed an abdominal compartment syndrome, with progressive hemodynamic compromise, for which an urgent laparotomy with splenectomy had to be performed. An image of the spleen after surgical removal is presented in Figure 2, showing the large splenic size and rupture of the capsule.

To our knowledge, this is the first reported case of a patient on ECMO with a spontaneous spleen rupture. Although there is not much information to be found about the effect of ECMO on splenic size, ECMO does not seem to be a significant risk factor for splenic rupture. Klippenstein et al. reviewed the effect of ECMO on spleen and liver size in neonates.
Splenic volumes increased significantly in all 7 patients, while hepatic size did not. While this is a very small study and might not be extrapolated to an adult population, it could suggest that ECMO can lead to an increase in splenomegaly. One possible explanation is that hemolysis and platelet activation in the ECMO circuit could lead to splenic sequestration, resulting in an increase in splenic volume.

Our patient was being treated with a combination of Ruxolitinib and a BET-inhibitor for his myelofibrosis. BET-inhibitors regulate transcription of (onco-)genes, which could lead to thrombocytopenia [19]. Therefore the BET-inhibitor could have played a role in the thrombocytopenia of our patient and his subsequent therapy-interruption. However, it does not have a direct influence on the immunologic system and cytokines and there are no reports of ARDS or septic-like shock syndromes after discontinuation of a BET-inhibitor. We therefore believe that it did not play a role in the discontinuation syndrome and cytokine storm. Invasive pulmonary aspergillosis and staphylococcal toxic shock syndrome certainly were late fatal septic events that accelerated the demise of the patient.

4. Conclusion

Ruxolitinib discontinuation syndrome is a rare syndrome in the ICU. However, JAK-inhibitor therapy is now approved for myelofibrosis and polycythaemia vera patients resistant to hydroxyurea treatment and is being prescribed more frequently. Studies have shown that sudden cessation of ruxolitinib therapy should be avoided, due to the increased risk of withdrawal syndrome and worse outcome [8].

Even with tapering of RUX dose, a withdrawal syndrome can occur. It is important to recognize this syndrome early given the dramatic presentation with possible fast deterioration, especially when there is a good prognosis with timely restart of JAK-inhibitor therapy and corticosteroids. Restarting at a tapering dose, with or without corticosteroids will usually result in a quick clinical improvement, with limited side effects. Intensivists should be aware of this syndrome.

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