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# Ruxolitinib withdrawal complicating emergency aortic root replacement

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## Abstract

Ruxolitinib, a Janus kinase inhibitor, is associated with severe withdrawal phenomena. Adequate tapering is often underemphasized in surgical emergencies and can complicate the postoperative course. We present a case of acute ruxolitinib withdrawal in a gentleman undergoing emergency cardiac surgery

**Keywords:** Ruxolitinib • Aortic syndrome • Cardiac surgery

## INTRODUCTION

Ruxolitinib is a type one selective adenosine triphosphate competitive inhibitor of Janus kinase (JAK) 1 and 2 receptors [1]. It binds and stabilizes the kinase active conformation thereby inducing accumulation of phosphorylated JAK [1]. This causes inhibition of signal transduction activator of transcription (STAT) phosphorylation and reduction in cytokine-mediated symptoms [1, 2]. It is a common treatment in myelofibrosis and recently in cases of severe coronavirus infection [1, 2].

When ruxolitinib is rapidly withdrawn, recrudescence of cytokine-mediated symptoms occurs from immune hyperactivation [1, 3]. The accumulated JAK induced by ruxolitinib has an activation loop conformational change protective against signalling deactivation and sensitizing to extrinsic inflammatory signalling [3]. The hypercytokinaemia perpetuates a pro-inflammatory and pro-coagulopathic feedback loop whose manifestations are akin to severe pro-inflammatory states (including coronavirus) and post bypass vasoplegia [2, 4]. Ruxolitinib discontinuation syndrome (RDS) is a diagnosis of exclusion [1]. Case reports have conveyed variable onset times from 24 h to 2 weeks after cessation [1, 4].

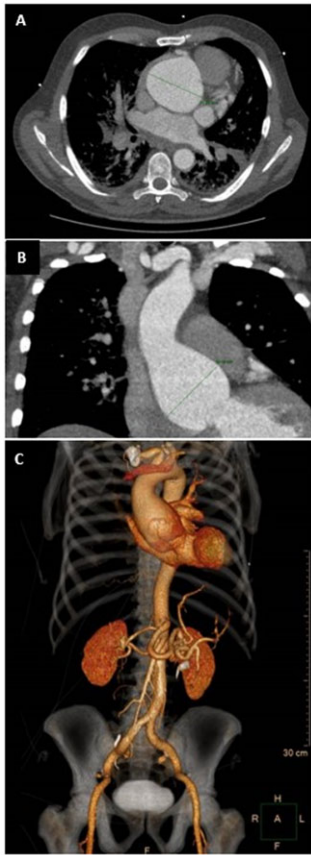
We describe a unique experience in emergency cardiac surgery where post bypass vasoplegia, myocardial stunning and coagulopathy impacted diagnosis of RDS and outcome [3].

## CASE REPORT

A 58-year-old gentleman with myelofibrosis presented to emergency with central chest pain. His regular medications were ruxolitinib, aspirin and clopidogrel. Of note, he had aspirated pond water a few days prior to presenting. On arrival, he was

haemodynamically stable but febrile. Echocardiogram (ECG) was unremarkable, C-reactive protein (CRP) <2 mg/l, white cell count (WCC)  $31 \times 10^9/l$ , platelets  $602 \times 10^9/l$ . Troponin T was 45 ng/l, D dimer 0.27 mg/l, INR 1.2, rapid coronavirus swab negative, pro-B-type natriuretic peptide (BNP) 2286 ng/l, atypical pneumonia and septic screen were negative. Computed tomography (CT) aortogram demonstrated severe aortic annulus and sinotubular junction dilatation to 69 mm with diffuse interstitial oedema (Fig. 1). Echocardiography demonstrated torrential functional aortic regurgitation secondary to aortic aneurysmal dilatation. As such, the recommended treatment is urgent surgical management. Preoperative haematology opinion was sought to assess the patients 12-month myelofibrosis prognosis and surgical considerations. A recommendation to proceed to surgery and recommence Ruxolitinib at the earliest convenience accepting a higher perioperative risk of infection was made by haematology. No discussion of anticipated RDS was had.

Following 24 h of empirical antibiotic treatment, and considering the high aortic rupture risk, he underwent an aortic root replacement with 32-mm Gelweave™ Valsalva interposition graft (Sulzer Vascutek, Renfrewshire, Scotland) and 29-mm Inspiris aortic valve replacement (Edwards, CA, USA) the following day with 68 000 units of heparin administered for cardiopulmonary bypass. Intraoperatively heparin resistance and aspiration were suspected and broad-spectrum antibiotics were initiated and continued postoperatively. Ruxolitinib was recommenced on postoperative Day 3. On Day 7, he developed right arm weakness, hypoxia, deteriorating Glasgow Coma Scale, mixed septic/cardiogenic shock and new inferolateral ST elevation with troponin rise. CT brain was unremarkable, CT aortogram excluded aortic dissection but noted a filling defect in the proximal right coronary artery, CT pulmonary angiography showed lobar pulmonary embolus, coronary



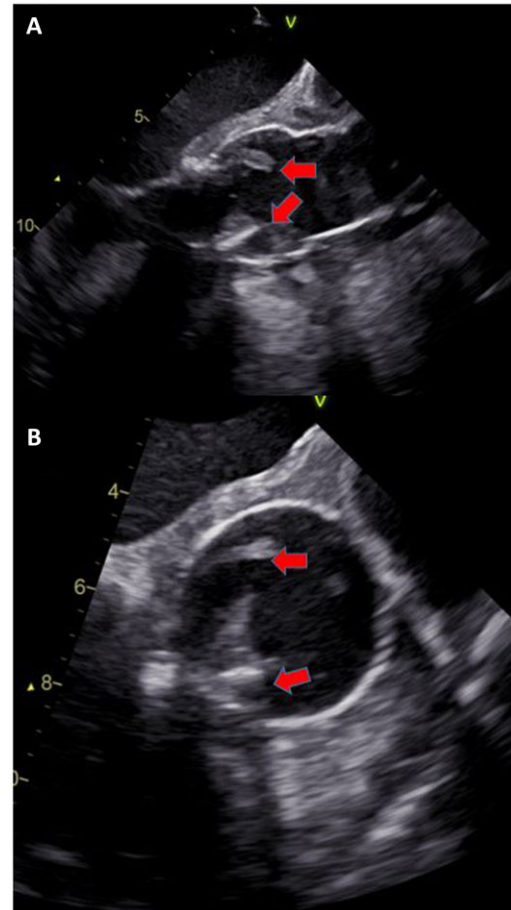
**Figure 1:** Preoperative computed tomography angiography (A) axial (B) coronal and (C) 3D reconstruction.

angiography was normal. Subsequent echocardiography demonstrated new moderate-severe biventricular failure and aortic root thrombus with intermittent occlusion of the coronary ostia (Fig. 2). Differential diagnosis included septic cardiomyopathy, systemic inflammatory response syndrome, heparin induced thrombocytopenia, myelofibrosis thrombosis due to elevated cell counts. The 4T score was intermediate for heparin induced thrombocytopenia, heparin-dependent platelet antibody was negative and the patient was commenced on a heparin infusion.

Consultant haematology opinion was again sought at which time RDS was suggested as a differential diagnosis befitting the evolving clinical picture although sepsis was still considered more likely. Antibiotics were escalated, the patient was reintubated, intra-aortic balloon pump was inserted and 100 mg of IV Hydrocortisone QID was commenced. Tocilizumab was considered but not initiated as sepsis was deemed more likely. Cyto-reductive hydroxyurea was considered and deemed unacceptable risk of pancytopenia. At this time, his cardiac index was  $1.57 \text{ l/min}^2$ , venous saturations were 35% with noradrenaline at  $4.2 \mu\text{g/kg/h}$ , milrinone at  $6.6 \mu\text{g/kg/h}$  and adrenaline at  $4.2 \mu\text{g/kg/h}$ .

Thromboelastographic studies showed impaired endogenous fibrinolysis, and considering suspected heparin resistance activated partial thromboplastin time (APPT) targets were escalated and titration was guided by Anti-Xa. Monitoring discrepancies were attributed to diffuse factor consumption and anticoagulation was sequentially escalated to non-Antithrombin III agents (Tirofiban, Argatroban) to no avail.

Consideration was given to extracorporeal membrane oxygenation (ECMO) bridging, however, given his coagulopathy and



**Figure 2:** Postoperative trans-oesophageal echocardiogram of aortic valve and left ventricular outflow tract. Arrows depict clot abutting valve leaflets (A/B).

suspected heparin resistance there were significant concerns of circuit failure as well as worsening root stasis. Similarly, consideration of surgical clot extraction would require going back on bypass and likely veno-arterial (VA) ECMO post which would likely both worsen his biventricular failure and carry the additional aforementioned risks of ECMO.

Therefore, on balance of risks, a slow Alteplase infusion after consideration of the 2020 AHA mechanical valve anticoagulation guidelines and the PROMETEE Trial [5, 6]. Serial echocardiography showed no reduction in clot burden and progressive biventricular failure. He developed refractory ventricular arrhythmia due to progressive myocardial ischaemia and was palliated after a CT brain demonstrated multifocal infarcts.

The patient was appropriately treated for the likely differential diagnosis of sepsis, managed for post bypass vasoplegia, systemic inflammatory response syndrome, septic cardiomyopathy and adequately therapeutically anticoagulated, however, did not clinically respond as expected. By elimination, given temporal association with Ruxolitinib cessation, an absence of definitive cyto-reductive or immunosuppressive agents; retrospectively RDS was deemed a significant contributory diagnosis.

## DISCUSSION

The JAK-STAT pathway is a signalling pathway responsive to inflammatory cytokines and haematopoietic growth factors [1].

Type I/II cytokine binding causes dissociation of intracellular subunits, alleviating constitutive inhibition [1, 3, 4]. Ruxolitinib competitively inhibits JAK receptors but in doing so causes a conformational change that results in a ubiquitous pool of active phosphorylated JAK [1, 3, 4]. When the inhibitory stimulus of Ruxolitinib binding is removed, and the pool of active JAK/STAT is not mitigated by steroids or alternative immunomodulation; the result is immune hyperactivation [2–5]. This can mimic disseminated intravascular coagulation, sepsis, systemic inflammatory response syndrome acute respiratory distress and post bypass vasoplegic syndrome [2–4, 7].

The clinical consequences of under recognizing RDS, delaying alternative immunomodulation and the difficulty of managing RDS once established are well depicted by this case. Whilst RDS is a diagnosis of exclusion, in cases where there are confounding variables and multiple pathologies such as in the cardiac surgery cohort, making a diagnosis is difficult, which this case clearly highlights.

From our experience, if faced with a similar patient, we recommend the following: seeking prompt and continuous haematological multidisciplinary guidance, considering continuation of Ruxolitinib accepting a higher perioperative infection risk or considering early recommencement in *addition to* systemic steroid therapy after any period of Ruxolitinib cessation given poor oral bioavailability perioperatively. Furthermore, a high index of clinical suspicion is recommended and early deliberation of Tocilizumab is warranted if there is insufficient clinical response to standard therapy [1].

ECMO and bypass are fraught with coagulopathy considerations, among them heparin resistance. RDS not only mimics this but presents an additional consideration to the management algorithm as contemplation of cytoreductive or Tocilizumab therapy may have improved the response to anticoagulation and ultimately changed the outcome.

RDS and preoperative infection both contributed to this patient's outcome. Whilst the risk of delaying surgery and managing risk factors of aortic rupture until the patient recovered from a suspected respiratory tract infection was deemed unacceptable

in this case, future cases should consider the risk of RDS and its treatment in deciding on perioperative timing and optimization.

**Conflict of interest:** none declared.

## Reviewer information

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