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CASE IN POINT

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Ruxolitinib Withdrawal Syndrome in a Patient With Myelofibrosis and Myelodysplastic Syndrome

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A 61-year-old man presented to the emergency department (ED) with fevers, chills, and fatigue that had been ongoing for 2 days. The patient's medical history was significant for heart failure, reduced ejection fraction, aortic stenosis after transcutaneous aortic valve replacement, coronary artery disease, and recently diagnosed myelodysplastic syndrome with myelofibrosis (*JAK2* V617F mutation-positive).

History. The man's myelodysplastic syndrome with myelofibrosis had been discovered approximately 4 months prior to presentation after the results of a routine complete blood cell count had revealed mild pancytopenia. He then had undergone a bone marrow biopsy, the results of which showed consistent variable marrow cellularity, 60% erythroblasts with dyserythropoiesis, increasing ring sideroblasts, atypical megakaryocytic hyperplasia, and no blast cells. At baseline, the patient had normocytic hypochromic anemia, moderate thrombocytopenia, and slight lymphocytopenia. Treatment of his cytopenias was initially delayed secondary to his aortic valve replacement, but eventually ruxolitinib was initiated

approximately 1 month after the bone marrow biopsy.
Upon arrival in the ED, the patient reported that he had run out of his ruxolitinib medication 2 days ago, and that evening he had started feeling more fatigued. During the next 48 hours, the patient experienced more constitutional symptoms and continued to remain out of ruxolitinib. (The nearest medical center to him was more than 2 hours away; he thought that he could wait until his next oncology appointment 6 days later to refill his ruxolitinib prescription). He continued to take his other usual medications, which included atorvastatin, metoprolol, lisinopril, aspirin, and warfarin.

Physical examination. A review of systems was positive for a cough, malaise, nausea, and anorexia. Vital signs showed slight tachycardia but were otherwise unremarkable. On examination, the patient had a pallorous appearance and was in mild discomfort. Lung examination did not reveal any crackles, wheezing, or decreased breath sounds; cardiac examination revealed a systolic murmur that had been reported in prior documentation.

Diagnostic tests. The results of a renal function panel were significant for evidence of acute kidney injury, with a potassium level of 5.6 mEq/L and a creatinine level of 3.68 mg/dL, with normal values having been recorded 1 week prior. A complete blood count revealed worsening cytopenias with a hemoglobin level of 6.7 g/dL, a white blood cell (WBC) count of 9700/μL, and a platelet count of $107 \times 10^3/\mu$L. The patient had elevated liver function test results (aspartate aminotransferase [AST], 710 U/L; alanine aminotransferase [ALT], 547 U/L; alkaline phosphatase, 12 U/L; total bilirubin, 1.8 mg/dL), non-ST-elevation myocardial infarction (troponin, 3.18 ng/mL), a normal brain natriuretic protein (BNP) level of 78 ng/mL, coagulopathy (international normalized ratio, 1.8, partial thromboplastin time, 25 s), and a metabolic acidosis (lactate, 5.5 mg/dL).

Electrocardiography results were unchanged from baseline, showing normal sinus rhythm with Q waves present in the inferior leads and mild ST depression in the anterolateral leads. Chest radiography showed bilateral patchy airspace opacification. Given the significance of the laboratory test and imaging findings, the patient was initially treated as having sepsis secondary to community-acquired pneumonia.

Cultures were drawn, and he was started on intravenous (IV) fluids, ceftriaxone, and azithromycin. One unit of packed red blood cells was given. The patient's ruxolitinib, 5 mg twice daily, continued to be withheld as he was admitted to the hospital.

Hospital course. The patient remained hemodynamically stable throughout the night, and the lactate level trended downward the next morning with continued IV fluids. However, certain laboratory values worsened, and his overall clinical picture did not improve. The troponin level continued to rise, and a cardiologist was consulted for possible left-heart catheterization and a heparin drip, but neither were recommended given the patient's risk factors and current state. The AST level remained stable at 686 U/L, and the ALT level increased to 1118 U/L.

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Other causes of elevated liver enzymes were ruled out (eg, hepatitis, Epstein-Barr virus, cytomegalovirus), and abdominal ultrasonography findings were consistent with hepatocellular injury. Kidney function also worsened, with a creatinine level of 3.78 mg/dL. The WBC count, platelet count, and hemoglobin level also continued to worsen. Hemolysis laboratory tests and a blood smear were obtained, given his recent transcutaneous aortic valve replacement, but findings were unrevealing and negative for disseminated intravascular coagulation (DIC).

Hematology and oncology specialists were consulted the morning after admission for worsening cytopenias. It was hypothesized that the patient likely could be having a withdrawal syndrome from ruxolitinib. He was started on 80 mg of prednisone. In addition, ruxolitinib, 10 mg, was given once initially, then 5 mg twice daily thereafter. The following day, the patient's symptoms started to improve, and his laboratory test values started to trend in the correct direction. He was eventually discharged back on his usual 5 mg/day ruxolitinib regimen.

The patient made a full recovery and was seen in the hematology-oncology clinic 1 month after this episode. His platelet count, hemoglobin level, WBC count, creatinine level, troponin level, and liver enzymes all had returned to within the ranges before his hospitalization. He was instructed to make sure he did not miss any future doses of ruxolitinib and to contact the nearest medical center if he ran out of the medication.

Discussion. Cytokine release syndrome (CRS) is a systemic inflammatory response that can be triggered by a variety of infections and drugs, notably in immunotherapy.[1] The term was coined in early 1990s when muromonab-CD3 was introduced as an immunosuppressive treatment in solid organ transplant.[1]

The incidence of CRS depends significantly on the type and specific immunotherapeutic agent.[1] Few studies have been published reporting the incidence of CRS; most found that the incidence of CRS was greater than 50% in patients undergoing immunotherapy. Patients who underwent T-cell–related immunotherapy were found to have higher rates of CRS than those on standard monoclonal antibody therapy.[1]

CRS can present in numerous ways, from mild flulike illness (fever, fatigue, headache, rash, arthralgias, myalgias) to life-threatening multisystem organ failure (high fever, shock, DIC, tumor lysis).[1,2] Dyspnea, hypoxemia, and bilateral opacities on chest radiographs are common and can progress rapidly with the possible need for intubation in severe cases.[1] Laboratory abnormalities usually include cytopenias, elevated liver enzymes and creatinine, elevated inflammatory markers (erythrocyte sedimentation rate/C-reactive protein level), and elevated prothrombin time/partial thromboplastin time.[1]

The pathophysiology of CRS is still being investigated.[2] CRS is the summation of downstream effects of the binding of an antibody or T-cell receptor to its antigen.[2] This binding leads to

activation of all cells involved in the immune response and those not involved in the immune response, such as endothelial cells.[2] Activation of these nearby cells results in a cytokine efflux, with the most common being Interleukin (IL) 6, IL-10, and interferon-γ.[2]

Ruxolitinib is an ATP-mimetic JAK1 and JAK2 inhibitor and was one of the first JAK inhibitors to be evaluated as treatment for myelofibrosis.[3] Ruxolitinib works via the JAK-STAT signaling pathway and induces JAK-2 loop phosphorylation and prevents further ubiquitination and degradation of JAK.[4] When this signaling pathway is disturbed, as in ruxolitinib withdrawal syndrome, there is a rebound effect from increased phosphorylation of JAK-2 leading to degradation of JAK and a massive immune response as a result of this disruption in signaling.[4]

CRS is graded on a scale of 1 to 4, with 1 being the least serious, including only fever and constitutional symptoms, and grade 4 being the most serious, requiring mechanical ventilation and with grade-4 organ toxicities.[5] CRS can mimic tumor lysis syndrome and severe sepsis due to each being widespread systemic inflammatory reactions.[2,5] Individuals with CRS are at high risk of bacterial or viral infection, usually involving the respiratory tract.[5] These individuals should still be worked up for sepsis in order to avoid life-threatening infection after CRS, when the body's immune system is at one of its weakest points.

Patients with grade 1 CRS usually require supportive care in addition to treatment of fever and neutropenia.[5] Patients with grade 2 CRS or those with hypotension and hypoxia also require supportive care, but those with extensive comorbidities or who are older than 65 years require treatment similar to that of grade 3 or 4 CRS. The usual treatment of grade 3 and 4 CRS is supportive care, corticosteroids, and tocilizumab.[5] Tocilizumab is an anti–human monoclonal antibody that is typically used for the treatment of rheumatoid arthritis and other autoimmune diseases but has been shown to prevent IL-6 activation and binding and thus can be used to treat life-threatening CRS.[5] Multiple doses of the medications are sometimes needed to achieve a response.[5] In addition, acute respiratory distress syndrome (ARDS) should be ruled out prior to concluding that CRS is the cause.[6] An ARDS diagnosis was a consideration in our patient's case, given his abrupt hypoxia and normal BNP level with bilateral chest infiltrates on radiographs.

Ruxolitinib is rapidly absorbed, can reach maximal concentration in less than 1 hour, and has a half-life from 2 to 6 hours.[1] Few case reports in the literature describe ruxolitinib discontinuation syndrome. Ruxolitinib withdrawal syndrome can occur within 24 hours to 3 weeks after discontinuation of the drug.[2] Our patient presented 48 hours after abrupt discontinuation of the drug, and his condition continued to deteriorate over the next 48 hours. In a 2011 Mayo Clinic report,[3] ruxolitinib was discontinued in 47 patients with myelofibrosis after a median treatment time of 9.2 months due to various reasons. As a result, most patients had acute relapse of symptoms and splenomegaly during the discontinuation phase. One patient developed mild

anemia and worsening renal function, and the ruxolitinib dosage was halved. Following this change, the patient developed what a septic shocklike syndrome with severe hypoxia, fever, and confusion. Similar to our patient's case, ruxolitinib was restarted along with systemic corticosteroids, and the patient, who had been intubated, improved dramatically and was extubated. Another patient described in the Mayo Clinic report developed a pleural effusion and pericardial effusion after abrupt tapering of the ruxolitinib dosage.

Other results of ruxolitinib withdrawal syndrome described in the literature include rapid spleen volume enlargement, splenic infarction, and tumor-lysis–like syndrome.[1,2] Based on the severity of the clinical picture, it was determined that our patient developed a grade 2 CRS reaction.

With increasing use of immunotherapy and the increase in associated autoimmune adverse effects, there is an urgent need for clinical trials to improve upon the diagnosis, treatment, and prevention of CRS. At this time, ruxolitinib withdrawal syndrome is a diagnosis of exclusion. The development of biomarkers specific for CRS, similar to troponin, would indicate how well the immune system is functioning. Treatment remains mainly supportive in most instances, along with corticosteroids in severe cases such as that of our patient. Prevention of ruxolitinib withdrawal syndrome is not standardized. Current strategies include the use of corticosteroids before drug discontinuation and slow tapering of ruxolitinib.[3]

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