A Fatal Case of Ruxolitinib Discontinuation Syndrome Preceded by Hypercalcemia

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Ruxolitinib is an inhibitor of the cytosolic tyrosine kinase Janus kinase (JAK) family of proteins (JAK1/2), which is widely used to treat various myeloid neoplasms that are characterized by constant activation of the JAK-STAT signaling pathway.Many side effects are associated with ruxolitinib, including anemia, thrombocytopenia, increased rate of infections (especially herpes zoster), and mild hypercalcemia noted in 15.4% of patients [1]. The possible mechanism causing hypercalcemia may involve altered bone and mineral metabolism with secondary hyperparathyroidism, as described for other kinase inhibitors [2].

Life-threatening adverse events including respiratory distress, septic-like shock, and disseminated intravascular coagulation-like syndrome may occur after ruxolitinib discontinuation. These events, attributed to an acute rebound of cytokine storm, were defined as ruxolitinib discontinuation syndrome (RDS) [3]. Careful down tapering was suggested as a preventive strategy of RDS, although a few cases were reported even when using this strategy. Based on the biggest cohort to date [3], RDS typically presents within 3 weeks (median 7 days, range 2–21) of ruxolitinib discontinuation, apparently with no relation to ruxolitinib dose, and seems to improve after ruxolitinib re-introduction. The syndrome occurs in 13.5% of patients who discontinue the drug. The mild form presents with increased spleen size and constitutional symptoms. It is seven times more prevalent than the severe form. Severe RDS was reported in only three cases, each of them unique. One patient presented with a spleen rupture; another with fever, dyspnea, confusion, and dizziness requiring hospitalization; and a third with acute respiratory distress syndrome, treated in the intensive care unit. Overall, severe RDS occurred within 48 hours after the drug was stopped, and all patients rapidly improved after the ruxolitinib rechallenge.

We describe a case of severe hypercalcemia developed during ruxolitinib therapy, resulting in therapy discontinuation and fatal RDS.

PATIENT DESCRIPTION

A 65-year-old male was admitted to the emergency department after 2 weeks of non-specific symptoms, including weakness and loss of appetite and weight. On admission, he had borderline hypotension and a low body temperature of 34.5°C. His past medical history included a JAK2 positive myelodysplastic syndrome/myeloproliferative neoplasm (MDS/MPN). He presented with anemia and received regular blood transfusions with iron chelation and an erythropoietin-stimulating agent. In the 8 months prior, he had been treated with ruxolitinib, with a good response. His other medical conditions included ischemic heart disease, atrial fibrillation, a previous stroke, peripheral vascular disease, diabetes, and smoking.

The initial workup in the emergency department did not reveal the source of the complaints. His blood count was normal except for mild chronic anemia of 10.7 g/dl. Blood chemistry showed normal glucose, creatinine, sodium, and potassium levels, whereas C-reactive protein was slightly elevated at 20 mg/L. Chest X-ray and urine dipstick did not support an infection. The patient was treated empirically with ceftriaxone and fluids and hospitalized in an internal medicine department.

Following his admission, the patient became stuporous and febrile up to 40.8°C. His serum calcium was 14.2 mg/dl and rose to 16 mg/dl (normal 8.6–10.3 mg/dl) accompanied by normal phosphate levels and elevated PTH of 31.2 pmol/L (normal 1.6–6.9 pmol/L). The hypercalcemia was successfully normalized by aggressive rehydration, diuretic therapy, and pamidronate. Yet, the patient did not regain consciousness. A non-contrast brain computed tomography (CT) and a lumbar puncture were normal including negative polymerase chain reaction tests of herpes and JC viruses.

During the few next days, the patient went into shock with multiple organ failure and his Hb level dropped to 6.1 g/dl necessitating blood transfusions. Ferritin level was extremely elevated at 7000 mcg/L (normal 24–336 mcg/L) with a transferrin saturation of 46%. A peripheral blood smear revealed no sign of malignant transformation. Blood and urine cultures were sterile, total body CT found no source of infection, and several antibiotic treatments, including ceftriaxone, meropenem, and piperacillin/tazobactam, did

not improve the patient's condition.

On the ninth day of hospitalization, the patient went into respiratory distress, accompanied by hemodynamic instability. Resuscitation efforts failed and he died.

COMMENT

Our patient presented with a septic-like shock condition, including fever, hypotension, decreased level of consciousness, and multi-organ failure in addition to hypercalcemia and extreme elevation of serum ferritin levels. Despite a fast correction of the hypercalcemia, he continued to deteriorate, both cognitively and hemodynamically until his death several days after his arrival.

His prominent hypercalcemia may be explained by two scenarios. The first is a parathyroid crisis and the second is an adverse reaction to ruxolitinib. Primary hyperparathyroidism can occur at all ages with a peak incidence in the sixth decade. The most common presentation of this disorder is an incidental asymptomatic disease found in biochemical screening tests. A rare presentation, called parathyroid crisis, fits more with our patient, as it is characterized by severe symptomatic hypercalcemia [4]. It appears more in the context of a severe illness, volume depletion, or infarction of a parathyroid adenoma. Two findings make this diagnosis less likely in this patient. The first is a normal level of calcium recorded two months before admission and the second is a lack of bone and renal involvement according to the imaging performed. Both are not suggestive of chronic primary hyperparathyroidism.

Drugs are another major cause of hyperparathyroidism. Our patient did not take the most familiar drugs associated with the disorder (e.g., thiazide diuretics and lithium). However, he was recently treated with ruxolitinib, which commonly causes hypercalcemia, although not this severe. The temporal relationship between the initiation of ruxolitinib therapy and hypercalcemia strongly suggested that ruxolitinib was the responsible agent. After the association was revealed, ruxolitinib was stopped for two days and then reinitiated at a dose of 5 mg twice a day, instead of 10 mg twice daily.

Ferritin is not only an intracellular iron storage protein but also a known acute-phase reactant with a role in orchestrating cellular defense against oxidative stress and inflammation. A chronic iron overload is characterized by elevated ferritin, but it was ruled out as the cause of hyperferritinemia in our case, as the ferritin level measured three months before admission was approximately 800 mcg/L, reflecting only a chronic modest elevation. Only a few disorders are associated with such extremely high ferritin levels, including the life-threatening syndrome of excessive immune activation namely hemophagocytic lymphohistiocytosis (HLH), macrophage activation syndromes, certain rheumatologic disorders (e.g., Still's disease, systemic juvenile idiopathic arthritis), certain cancers (mostly hematological), and fulminant liver failure. In support of the HLH diagnosis was the presentation with fever and mental state changes, hyperferritinemia, and to some degree liver injury. Meanwhile, the patient lacked certain features that are very common in HLH and did not fulfill the HLH-2004 criteria. Specifically, he had cytopenia of a single cell line only, no hypertriglyceridemia, and no splenomegaly. Thus, HLH was unlikely all the more so because the patient previously received ruxolitinib, which is reported as an effective salvage therapy for HLH [5]. Ruxolitinib downregulates the HLH-associated cytokine storm while ruxolitinib discontinuation can mimic HLH by inducing a cytokine storm presenting as a septic-like condition. RDS was the most likely explanation for our patient's sudden deterioration after it was determined that a few weeks before his admission he became confused and stopped taking his medications, including ruxolitinib.

Thus, the following chain of events may have led to the patient's demise. First, ruxolitinib therapy induced hypercalcemia, causing mental deterioration and discontinuation of ruxolitinib. Later, RDS developed, manifesting as a septic-like condition. The reinstitution of ruxolitinib was unfortunately too late and incomplete and did not prevent the fatal deterioration.

To the best of our knowledge, our case is the first in which treatment with ruxolitinib was associated with such severe hypercalcemia. This result calls for further research on hypercalcemia caused by ruxolitinib and the causative biological pathway. Another important finding is that we may be the first to report extreme hyperferritinemia in RDS.

CONCLUSIONS

Management of ruxolitinib-associated complications should prompt a gradual tapering of ruxolitinib dose rather than abrupt discontinuation, in addition to monitoring the development of a discontinuation syndrome. When signs of the syndrome become evident, it is crucial to return to the original dose.

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