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Cover Page Footnote

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Case Report

Richter Transformation in Chronic Lymphocytic Leukemia with Hypercalcemia and Acute Kidney Injury Presenting as Altered Mental Status: A Case Report

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INTRODUCTION

Richter's transformation is a rare but extremely serious complication of underlying chronic lymphocytic leukemia/small lymphocytic leukemia (CLL/SLL), where an aggressive large B-cell lymphoma develops. The most common presentations are characterized by sudden clincal decline and diffuse lymphadenopathy, splenomegaly and worsening B symptoms. Lab values often demonstrate an increase in LDH, anemia and thrombocytopenia.[1] Richter's transformation has a very poor prognosis due to the severity of clinical decline.[2] Further analysis and pathological evaluation consisting of immunohistochemistry, flow cytometry, and genetic and molecular testing is often needed to identify cell markers or surface proteins that help direct treatment of the condition more appropriately.[1] Here, we depict a case of a patient undergoing a Richter's transformation with a presenting complaint of altered mental status and recent fall in the setting of hypercalcemia, unique presenting features for this condition.

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CASE PRESENTATION

A seventy-four year old female with a past medical history significant for CLL presented with complaints of confusion, fall, and shortness of breath. In the emergency department her heart rate was elevated to 102 beats per minute, and respiratory rate was 26 breaths per minute, with oxygen saturation of 95% on 4L. On physical exam she had significant bilateral submandibular and cervical adenopathy and bilateral decreased breath sounds. Initial labs demonstrated a WBC count of 25.1 x 103 μL−1 (4.0-10.0), a calcium of 15.0 mg/dL (9.0 –10.5) corrected to 15.9, and creatinine of 1.83 mg/dL (0.7-1.3). Hemoglobin (Hb) was found to be 8.5 g/dL (12-16), platelets were 116 x 103 μL−1 (150-350), and PTH was < 4.0 pg/mL. A peripheral blood smear showed evidence of smudge cells. Imaging revealed a soft tissue mass in the paratracheal region measuring 5.0 x 3.8 cm and bilateral paratracheal lymphadenopathy, along with extensive upper abdominal lymphadenopathy, splenomegaly and left lower lobe pulmonary nodules. The patient was given calcitonin, pamidronate, and aggressive intravenous fluid hydration. The patient's calcium was improving with intravenous fluids but creatinine was elevated to 2.13 mg/dL. Uric acid and LDH were found to be elevated at 9.9 mg/dL (2.5-8) and 351 U/L (60-100) respectively. At this time it was noted that Hb had dropped to 6.5 g/dL. She was then given a pure RBC transfusion, rasburicase, pamidronate and IVF infusion, with calcium lowering further to 11.5 mg/dL, creatinine improving to 2.01 mg/dL, Hb improving to 7.8 g/dL and uric acid improving to 6.2 mg/dL. Labs failed to improve on subsequent days of admission, with Hb once again lowering back to 6.8 g/dL, creatinine steady at 2.0 mg/dL, platelets dropping to 45 x 103 μL−1, and uric acid increasing to 7.0 mg/dL. A lymph node biopsy was then performed. Greater deterioration of the patient was seen after the lymph node biopsy, as uric acid increased to 9.9 mg/dL (another dose of rasburicase was given),

creatinine holding at 2.0 mg/dL, Hb 6.6, g/dL LDH 250 U/L, Fibrinogen <100 mg/dL, platelets at 18 x 103 µL−1, PT of 16s (11 – 13.5) and aPTT of 38s (25 – 35). She was subsequently tested for COVID-19, and the results were positive. The pathology results showed that the lymph node architecture was effaced by a diffuse and nodular proliferation of predominantly large pleomorphic lymphocytes positive for CD20 and MUM-1 (a non-GCB marker), with 100% positivity for BCL2, and a small background of B-cell lymphocytic leukemia. These results demonstrated evidence of diffuse large B-cell lymphoma, and was further described in the pathology report as non-germinal center type due to absence of CD10 marker and BCL6 marker on immunohistochemistry. Cytogenetics and fluoresence in situ hybridization (FISH) showed negative results for FMC7, IgVH, Cyclin-D1, 17p deletion, trisomy 12, 11q deletion and 6q deletion. Flow Cytometry showed negative results for CD5 and CD23. The phenotypic results were positive for 13q deletion. This confirmed the suspicion of this patient undergoing a Richter's transformation.

DISCUSSION AND CONCLUSIONS

CLL is a form of leukemia that is considered to have a good overall prognosis with respect to other blood-borne cancers, with a median survival rate of 83% at 5 years.[3,4] There are, however, certain mutations or markers that indicate a poorer prognosis with lower survival rate such as IgVH, ZAP70, CB38 and 17p deletion.[5,6,7] The most important of these is deletion of 17p, which encodes for p53 and is associated with the poorest outcomes in these patients. Deletion on 13q is relatively common and often indicates a much better prognosis.[8,9]

One of the feared complications for patients living with CLL is Richter's transformation, which is the development of an aggressive large B-cell lymphoma in the setting of CLL. This transformation typically presents with enlarging lymph nodes, prominent B symptoms such as fever, night sweats and weight loss, and extranodal involvement usually of the skin, stomach, eyes and lungs.[5,6] Our patient offers a unique presentation of this disease state due to the lack of other underlying symptoms and signs, beyond enlarging lymph nodes, that are common to Richter's transformation. This patient presented with altered mental status that was a product of her underlying hypercalcemia and AKI, that were brought about by her transformation. These aspects can add value to the current literature and serve as additional symptoms for physicians to be cautious of when Richter's transformation is on their differential. Compounding effects of having COVID, causing the patient to suffer from DIC, also make this a unique case and serve as an obstacle for differentiating what features are attributable to a Richter's transformation, especially in the setting of the COVID pandemic.

Richter's transformation has an incidence rate reported in the literature to be 0.5-1% per year, but that value can be as high as 4-20% in previously treated patients. Overall, the ten year annual incidence rate is about 5%, with the value raising to 15% in those who have previously been treated.[6,10,11] Increased risk for this severe complication is associated with previous treatment using Bruton Tyrosine Kinase (BTK) inhibitors, presence of stereotype B-cell receptor, genetic findings such as: IGHV, ZAP70, CD39, CD40 and Notch 1 mutations, bulky lymphadenopathy, Hb <10 g/dL and LDH > 205 U/L at presentation.[12,13] In patients with a remote history of CLL and acute changes in their functional status, physicians should be on the lookout for features of Richter transformation, since it has such high mortality associated with it. This patient presented with acute mental status changes and was subsequently found to have elevated uric acid, calcium and creatinine. CT imaging of the chest, abdomen and pelvis demonstrated diffuse and bulky lymphadenopathy, raising suspicion for Richter transformation even further. Lymph node biopsy confirmed a Richter's transformation. With an active Richter's transformation confirmed and evidence of elevated uric acid we could elucidate the etiology of this patient's hypercalcemia as being from tumor lysis. Although tumor lysis (TLS) is usually associated with low serum calcium levels, the literature has shown that hypercalcemia can be present in TLS and in 15% of large b-cell lymphomas there is evidence of hypercalcemia.[14,15] Humoral hypercalcemia of malignancy could have also been considered, but due to the symptoms the patient was experiencing and lab results that were obtained, this was less likely, although management for this condition would be similar to what was done for our patient.

In the setting of acute changes for a patient with a known history of CLL, it is important to recognize the clinical deterioration potentially leading to death these patients may be facing. In a patient with a Richter's transformation, COVID-19 induced DIC16 could be a potentially fatal concurrent condition as recent studies have shown that CLL patients are at increased risk of mortality if they are infected by COVID-19.[17] It is important to recognize the COVID status of patients with hematological conditions because it can produce further complications of the patient's primary condition, making the road to improvement much more difficult.

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