Rare Presentation of Recurrent Follicular Lymphoma as Hypercalcemia

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Background

Recurrence of Follicular lymphoma presenting as hypercalcemia is unusual. Hypercalcemia can be seen usually with aggressive lymphoma such as Diffuse B-cell lymphoma but is rare in patients with indolent lymphomas such as follicular.

Hypercalcemia driven by excess 1, 25 vitamin D accounts for approximately 1% of cases of hypercalcemia in malignancy (1).

Case Report

69-year-old Caucasian male with past medical history of grade 1, stage IV follicular lymphoma, diagnosed 15 years ago, treated with chemoimmunotherapy followed by rituximab maintenance for 2 years, presented with fatigue, decreased appetite, abdominal pain, unintentional weight loss for >10 pounds over 3 weeks. Physical exam was normal. Work up showed corrected calcium level of 13.5, with parathyroid hormone (PTH) suppressed at 5.6 pg/ml and absolute lymphocyte count of 5901 cells/mm3. Further work up showed normal 25 vitamin D, PTHrP and elevated 1, 25 vitamin D at 91 (normal range 18-72), normal ACE (Angiotensin converting enzyme) level. Peripheral blood flow cytometry did not show any clonal population of cells. Imaging negative for lymphadenopathy, pulmonary infiltrates, hepatosplenomegaly. NM whole Bone scan was negative for metastatic bone disease, and workup for monoclonal gammopathy was negative. Bone marrow biopsy demonstrated Atypical lymphoid aggregates, suspicious for bone marrow involvement by a histologically Indolent low-grade B-cell lymphoproliferative disorder. Hypercalcemia was unresponsive to Zoledronic acid but responded to prednisone 60 mg po daily x 5 days. Patient did not want to undergo further work up and treatment of lymphoma. Due to other multiple co morbidities, he was discharged on hospice.

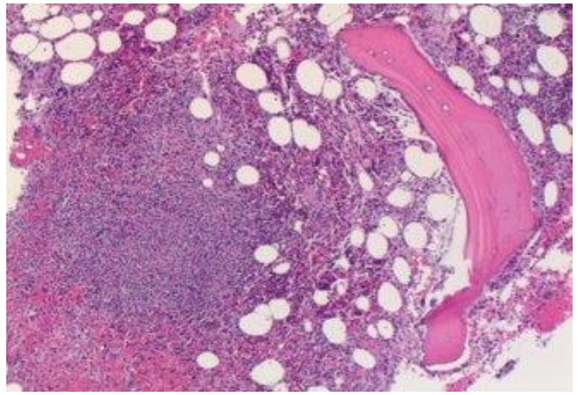

Figure 1: Interstitial nodular infiltration by small lymphocytes. Bone marrow core biopsy. H&E, X 100

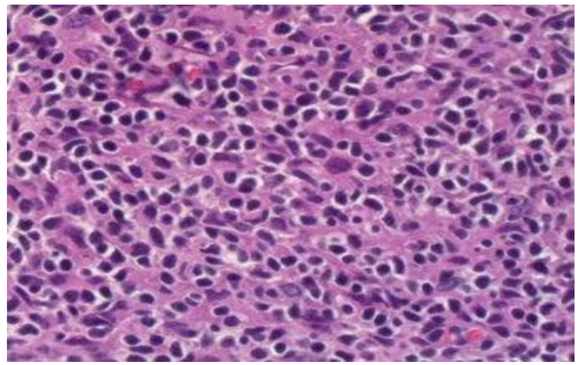

Figure 2: Small atypical lymphocytes with perinuclear clear cytoplasm. Bone marrow. H&E, X 630

Discussion

• Hypercalcemia of malignancy (HCM) is an important metabolic oncologic emergency and is the most common cause of hypercalcemia in hospitalized patients. HCM can occur in 20% of patients during their course of the disease and indicates a grave prognosis [1]. HCM usually presents with markedly elevated calcium with severe symptoms warranting hospitalization.

• Complex mechanisms were involved in the pathophysiology of HCM. Humoral hypercalcemia of malignancy is mediated by PTHrP as the common cause and accounts for 80% of cases. Osteolysis leading to release of local cytokines from tumor and resulting osteoclastic activity contributes to approximately 20% of cases. Less than 1% of cases are contributed by extrarenal production of 1,25 hydroxyvitamin D (calcitriol) and ectopic PTH production [1].

• Calcitriol mediated hypercalcemia is more common with aggressive lymphoma and most associated with Diffuse large B cell lymphoma [2]. Few case reports were found as such. It is less commonly associated with Indolent lymphomas such as follicular lymphoma. Only one case report found to our knowledge. It was reported in case series that Hypercalcemia in follicular lymphoma may indicate transformation to Diffuse Large B-Cell lymphoma (3).

• The treatment goal of HCM is centered on decreasing calcium levels and the treatment of underlying malignancy. Calcium levels can be decreased by conservative measures such as aggressive hydration, loop diuretics. Bisphosphonates are the mainstay of treatment; onset of action is late and has a long-lasting effect. Calcitonin onset of action is rapid but limited by tachyphylaxis. Bisphosphonates have revolutionized the treatment of hypercalcemia and are now widely available.

• Glucocorticoids are useful in treatment of hypercalcemia caused by calcitriol and multiple myeloma (4).

Conclusions

• Hypercalcemia with suppressed PTH and elevated 1,25 Vitamin D should always alert physician to thoroughly evaluate for granulomatous diseases and lymphomas. Hypercalcemia in lymphomas is mediated by extrarenal conversion of vitamin D 25 to calcitriol by 1-hydroxylase secreted by tumor associated macrophages (4) and respond to treatment with steroids hypercalcemia.

• Hypercalcemia can be a rare initial presentation of lymphoma and should be diagnosed promptly and treated appropriately.

References

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