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When Occam's Razor Fails: A Case of Concomitant Carcinoid and Sarcoidosis

To the Editor:

Skeletal metastases and humoral hypercalcemia of malignancy are commonly acknowledged causes of hypercalcemia in patients with cancer. However, nonmalignant causes of hypercalcemia also must be considered. We present a rare case of hypercalcemia in a patient with concomitant carcinoid and sarcoidosis.

CASE PRESENTATION

Our patient is a 75-year-old woman with carcinoid diagnosed from biopsies taken during a thoracoscopy in June 2009. Her symptoms of flushing and diarrhea were initially relieved with octreotide, but by July 2010 she started experiencing worsening hot flashes and back pain, and also was noted to have a calcium level of 10.9 mg/dL. Her performance status worsened until the winter of 2011, when she was hospitalized with fatigue, nausea, constipation, decreased appetite, excessive thirst, and generalized abdominal pain, in conjunction with a calcium level of 15.0 mg/dL. Treatment with aggressive intravenous fluids and zoledronate was initiated, but her symptoms and hypercalcemia persisted.

It was at this time that the patient presented to the Bassett Medical Center for further evaluation. A serum parathyroid hormone level was <10 pg/mL (normal 14-72 pg/mL), a serum parathyroid hormone-related protein level was 0.5 pmol/L (normal <2.0 pmol/L), and a bone scan was negative for metastases. Despite the absence of an elevated parathyroid hormone-related protein level, humoral hypercalcemia of malignancy was suspected on the basis of the presumption that humoral factors other than parathyroid hormone-related protein may mediate hypercalcemia. For this reason, her medication was switched from zoledronate to denosumab, a monoclonal antibody that targets receptor activator of nuclear factor kappa-B ligand. A reexamination of the original lung biopsy from 2009 also was undertaken, which revealed the presence of noncaseating granulomas and an elevated angiotensin-converting enzyme level. These findings, in conjunction with an elevated 1,25-dihydroxyvitamin D level of 105 pg/mL (normal 18-78 pg/mL), led to the concurrent diagnosis of sarcoidosis in this patient with preexisting carcinoid.

Octreotide continued to be administered to the patient because the results of a repeat computed tomography scan revealed innumerable splenic lesions suggestive of progressing carcinoid. She also was maintained on a dual regimen of denosumab and dexamethasone for adequate control of her hypercalcemia. As of October 2012, her calcium level was 7.9 mg/dL.

DISCUSSION

As physicians, we strive to pinpoint a patient's presenting symptoms with a single diagnosis. Although it is logical to associate hypercalcemia in patients with cancer with underlying malignancy, in doing so we may overlook nonmalignant causes.[1] We initially attributed our patient's hypercalcemia to carcinoid, and given the absence of bony metastases, we specifically suspected humoral hypercalcemia of malignancy. Although carcinoid is rarely associated with humoral hypercalcemia of malignancy,[2,3] it should be considered in patients with solid tumors but without skeletal metastases.[3] Parathyroid hormone-related protein is a common cause of humoral hypercalcemia of malignancy; however, there are many other circulating growth factors that may mediate hypercalcemia. Examples include receptor activator of nuclear factor kappa-B ligand, tumor necrosis factor-α and β, transforming growth factor-α and β, fibroblast growth factor 23, and interleukin-1 and 6. These factors are not routinely measured in standard laboratories, but in our patient, with low parathyroid hormone-related protein and elevated 1,25-hydroxyvitamin D levels, we presumed that other unidentifiable humoral factors were mediating her hypercalcemia.[2,4] Furthermore, reevaluation of our patient's original biopsy revealed the diagnosis of sarcoidosis. Despite there being few reported cases in the literature,[5] this finding raised the possibility of hypercalcemia being mediated by concomitant carcinoid and sarcoidosis.

CONCLUSIONS

Bisphosphonates counteract bone resorption in humoral hypercalcemia of malignancy via osteoclast inhibition. Monoclonal antibodies like denosumab also achieve osteoclast inhibition, but through the activation of receptor

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activator of nuclear factor kappa-B ligand. Denosumab may thus prove useful in cases of humoral hypercalcemia of malignancy refractory to bisphosphonates.

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