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CASE IN POINT

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Refractory Hypercalcemia in Nongranulomatous Disseminated Bacillus Calmette-Guérin Infection

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Intravesical administration of bacillus Calmette-Guérin (BCG) is a common adjunctive therapy in the treatment of superficial bladder cancer. BCG is a live attenuated strain of *Mycobacterium bovis*,[1] and as a result of intravesical BCG immunotherapy, local and systemic infectious and noninfectious complications can arise.

Pathogenic theories for infectious complications allude to a hypersensitivity reaction, with presence of granulomas and absence of recoverable organisms, as opposed to ongoing active infection with viable organisms found in a variety of tissues including lung, liver, pancreas, and the brain.[2] Among the most serious complications of BCG intravesical instillation are disseminated BCG infections, the hallmark manifestation of which is granulomas.

No consensus exists about diagnostic criteria for disseminated BCG infection. Bernatowska and colleagues[2] drafted suggested criteria that include systemic symptoms, laboratory criteria identifying *M bovis* BCG substrain, and histopathologic changes with granulomatous inflammation. Hypercalcemia and its sequelae can occur secondary to the granulomatous disorders, relating to the dysregulated production of 1,25-dihydroxyvitamin D by activated macrophages trapped in pulmonary alveoli and granulomatous inflammation.[3]

We present a case of refractory hypercalcemia due to disseminated BCG, without evidence of granulomas, in an elderly man who received BCG immunotherapy for transitional cell carcinoma (TCC).

CASE REPORT

The patient is a 75-year-old man with a history of an ascending aortic aneurysm (AAA), for which he had undergone surgical graft repair, and noninvasive papillary TCC of the bladder, for which he had been treated with 6 years of intravesical BCG.

The man presented to the hospital 6 months after his last intravesical BCG instillation with concern for a 3-month history of malaise, gait instability, micrographia, hoarseness, weight loss, fevers with a temperature up to 38.6°C, and night sweats. On physical examination, he appeared fatigued and deconditioned but had no nonfocal deficits on neurologic examination.

Results of initial laboratory tests revealed hypercalcemia, with a total calcium level of 11 mg/dL (reference range, 8.5-10.5 mg/dL), corrected for an albumin level of 2.6 g/dL (reference range, 3.8-5.3 g/dL). Laboratory test results were also significant for a potassium level of 2.3 mEq/L (reference range, 3.5-5.0 mEq/L) and elevated κ and λ light chains with a normal ratio without a paraprotein or M-protein spike.

An extensive workup of his hypercalcemia revealed low parathyroid hormone (PTH) and PTH-related peptide (PTHrP) levels and normal 1,25 dihydroxyvitamin D and 25-hydroxyvitamin D levels. Results of an interferon-γ release assay were negative for tuberculosis (TB). Findings of magnetic resonance imaging of the brain and spine, computed tomography scans of the chest, abdomen, and pelvis, and ultrasonography of the right upper quadrant were all negative for granulomatous disease. He received intravenous fluids and electrolyte replacement and was discharged.

The patient returned to the hospital 2 months later with a rapid decline in functional status and symptoms similar to those of the earlier episode. He again was found to have severe hypercalcemia. A repeated workup again revealed low PTH and PTHrP levels, and normal levels of angiotensin-converting enzyme (ACE), 1-α hydroxylase, and vitamin D levels. He was given intravenous fluids and bisphosphonate therapy and was discharged with normalized laboratory test values.

He again returned to the hospital a third time 2 months later (4 months after initial presentation) with similar symptoms. This time, he was seen by a urologist and underwent cystoscopy, the results of which showed 2 subcentimeter bladder tumors that were noninvasive and low-grade in appearance. Pathological analysis of a biopsy specimen confirmed the presence of low-grade noninvasive papillary urothelial carcinoma without extension into the detrusor muscle. There was no histologic evidence of granulomas in the bladder. The patient also underwent a bone marrow biopsy, the findings of which were negative for any granulomas or cancers.

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Additional imaging obtained in the hospital showed an incidental finding of a progression in size of his AAA (from 5.6 cm to 6.2 cm over a 2.5-month period), but no endovascular leak. Given concern for the AAA being an occult source of granuloma, the location was also investigated as a source of infection. A nuclear medicine white blood cell (WBC) scan showed no radiotracer uptake in this or any other region of the body. The area of endovascular repair was high risk and thus not amenable to biopsy.

On a fourth admission, the man's condition had worsened and resulted in hypoxemic respiratory failure, requiring intensive-care unit monitoring. He was found to have severe bilateral interstitial infiltrates. He initially was placed on antibiotics for hospital-acquired pneumonia. An consulting infectious disease specialist suspected disseminated granulomatous disease, based on the clinical timeline and the hypercalcemia. A bronchoscopy was done during this hospital stay.

He was discharged on a regimen of isoniazid, rifampin, and ethambutol, based on high clinical suspicion for granulomatous disease despite of the lack of histologic evidence of granulomas. Results of an acid-fast bacilli smear and a nucleic acid amplification assay were both negative for TB. He remained on empiric treatment with the antibiotics, a corticosteroid taper of prednisone, and vitamin B_6. After discharge, blood cultures grew *Mycobacterium tuberculosis* complex, consistent with a BCG strain, further strengthening the working diagnosis of disseminated BCG infection.

Months into treatment, the patient reported weight gain and improvement in strength with ability to perform activities of daily living. He completed a corticosteroid taper with further improvement of his respiratory tract symptoms. Results of imaging studies showed complete resolution of interstitial infiltrates, and he no longer required home oxygen.

DISCUSSION

The patient's initial presentation was consistent with disseminated BCG infection based on his systemic syndrome that was compatible with mycobacterial disease and diagnostic test results that eventually yielded evidence of bloodborne mycobacteria (BCG strain) in the setting of known history of BCG treatment.

Disseminated BCG infection after treatment with intravesical BCG immunotherapy is an uncommon but well-documented complication. Our patient also presented with severe refractory hypercalcemia in the acute phase of his illness. The proposed mechanisms of hypercalcemia in disseminated BCG hinge on granuloma formation as a driver, with granulomas being one of the characteristic findings of disseminated BCG infection.[3] The mechanism of hypercalcemia in granulomatous disease involves elevated extrarenal 25-hydroxyvitamin D 1α-hydroxylase activity in granuloma tissue macrophages, leading to increased serum 1,25-dihydroxyvitamin D levels. Autonomous extrarenal 1α-hydroxylase,

unlike native renal 1α-hydroxylase, is resistant to normal feedback controls, resulting in pathologically elevated serum calcium.[4]

Extensive testing was performed on our patient to look for evidence of concomitant granulomatous disease as is classically found in disseminated BCG; however, no such evidence was found via multiple radiologic imaging and biopsy investigations. Surrogate markers of granulomatous disease such as elevations in ACE and 1α-hydroxylase levels were all found to be normal. All radiologic, tissue specimen, and laboratory diagnostic test results supported nongranuloma-mediated hypercalcemia in the setting of disseminated BCG infection. Extensive workup to investigate other causes of hypercalcemia did not yield any clear etiology.

Our patient was treated with antimycobacterial agents and glucocorticoids, which are the standard therapy for disseminated BCG infection,[5] and had improvement. This case presents two important clinical findings: an atypical presentation of disseminated BCG infection where neither radiologic, nor tissue specimen, nor laboratory testing yielded evidence of granulomas, as well as what appears to be nongranulomatous disseminated BCG infection-mediated hypercalcemia, the mechanism for which is unknown. Multiple negative biopsies in the context of negative radiologic and laboratory test results made a compelling case for nongranulomatous disseminated BCG infection and nongranulomatous disseminated BCG infection-mediated hypercalcemia, neither of which have been previously reported.

LIMITATIONS

Clinical investigation for the presence of granulomatous disease in our patient consisted of radiologic testing, bladder mass and bone marrow biopsy, and laboratory testing for surrogate markers of granulomatous formation (1α-hydroxylase and ACE). All diagnostic modalities yielded negative results; however, studies such as a nuclear WBC scan may result in a false positive in the setting of granuloma formation or TB. It is also important to note that biopsy and microscopic identification are the definitive diagnostic means of granuloma identification[6]; however, the invasive nature of biopsy can limit the amount of investigative testing that can be performed.

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