

A Rare Manifestation of Neurovasculitis and Hemophagocytic Lymphohistiocytosis as a Late Complication of Bacillus Calmette-Guérin Administration

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Intravesicular administration of Bacillus Calmette-Guérin (BCG), a live attenuated strain of *Mycobacterium bovis*, has long been used as adjuvant therapy for treatment of non-muscle invasive bladder carcinoma. BCG is usually well tolerated; however, infectious complications can range from 1–5% of cases. Infectious complications of BCG [1] can be divided into localized disease, which is considered a late onset disease occurring 3 months following treatment such as cystitis, Epididymo-orchitis, and pyelonephritis. Another form is a systemic disease, which is an early onset manifestation including sepsis syndrome that usually occurs directly after treatment and is the most common form of disseminated BCG infection. Vascular involvement such as mycotic aneurism of the abdominal and thoracic aorta, hematological granulomatous bone marrow involvement, cytopenia, and hemophagocytic lymphohistiocytosis (HLH), in addition, small vessel vasculitis of the central nervous system (CNS) in rare cases and even meningitis. It is important to note that the sepsis syndrome can occur years after the last treatment in case of an immune system compromise leading to a reactivation of a dormant focus.

Our case of neurovasculitis and systemic HLH manifesting 2.5 years after the last course of treatment with BCG.

PATIENT DESCRIPTION

A 63-year-old patient with a medical history of transitional cell carcinoma (TCC) after transurethral resection of the bladder tumor (TUR) and six courses of BCG in 2019, ischemic heart disease following coronary artery bypass graft (CABG) in 2010 and a recent PTC along with heart failure and decreased ejection fraction with apical thrombus. A recent admission to another hospital with septic shock and negative blood culture, acute kidney injury and pancytopenia that later was complicated with central line bloodstream infection (CLABSI) and coagulase-negative Staphylococci (CoNS) bacteremia. Two days after hospital discharge, he presented with low blood pressure, fever, and weakness and was admitted into our department. On the first day of admission, physical exam was normal except for a palpable purpuric rash of the lower extremities; however, due to hemodynamic instability a central line was inserted. Initial blood work demonstrated pancytopenia with thrombocytopenia of 60k K/ μ L, ferritin 2272 ng/ml, acute on chronic renal failure and CRP 70 mg/L.

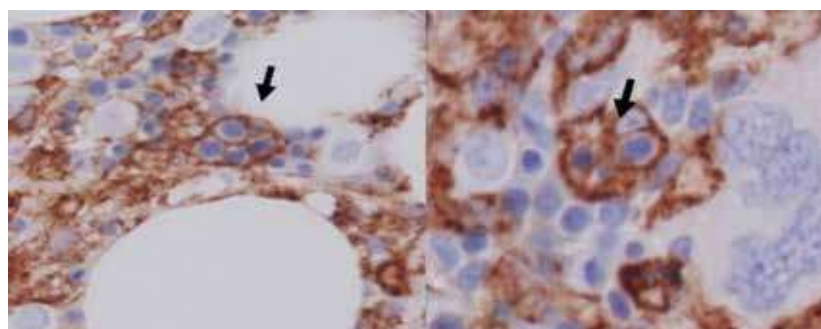
Due to the recent CoNS bacteremia endocarditis was suspected but vasculitis could not be ruled out due to a classical purpuric rash. As part of his workup, he underwent a skin biopsy that could not rule

out vasculopathy, and a cardiac echo that ruled out vegetations. In addition, due to increasing ferritin levels up to 19K ng/ml and triglycerides up to 550 mg/dl with increased soluble interleukin 2 receptor levels up to 6800 U/mL there was a clinical suspicion of HLH that was later proven by bone marrow biopsy showing numerous activated histiocytes with hemophagocytosis of red blood cells [Figure 1A].

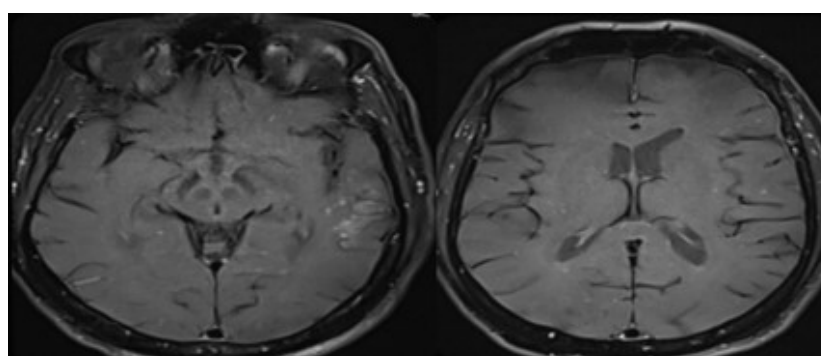
Three days after admission, our patient presented with confusion and mutism. Results of a brain computed tomography (CT) showed signs of a left temporal lobe stroke. To rule out shower emboli, our patient underwent a brain magnetic resonance imaging (MRI), which showed many pinpoint parenchymal lesions with no disruption of diffusion consistent with vasculitis of small blood vessels [Figure 1B]. The first suspected diagnosis was neurovasculitis. Another possibility was HLH of the central nervous system or intravascular lymphoma, which have similar MRI patterns. For his neurovasculitis he was treated with intravascular high dose solumedrol for 5 days followed by prednisone. A week after this treatment, a clinical and radiological improvement was noted. In a follow-up MRI a complete disappearance of the lesions was apparent.

After a short trial of steroid tapering, he underwent another regression with hemodynamic instability. A large abdominal hematoma was noted on his physical exam with an acute loss of hemoglobin. An abdominal CT showed severe pancreatitis. Due to this relapse, it was decided to switch treatment

Figure 1. Small vessel vasculitis of the CNS and HLH due to intravesicular BCG



[A] Bone marrow biopsy showing many activated histiocytes with hemophagocytosis of red cells (see arrows)



[B] A brain MRI with many pinpoint periventricular lesions with no disruption of diffusion consistent with vasculitis of small vessels

to high dose dexamethasone as intravascular lymphoma was still a potential cause for his HLH. Under steroid treatment he succeeded in reaching a form of stability. However, after transferring to the hematology department to be treated for his HLH, he died.

A month after the death of our patient bacteriology result from the skin biopsy came back positive with *Mycobacterium bovis* BCG.

COMMENT

BCG treatment is considered an integral part in the treatment of non-muscle invasive bladder carcinoma since it was first found to be useful in causing a strong inflammatory reaction in the healthy bladder of dogs in 1975 [2]. BCG instillation is considered to be the most successful cancer immunotherapy to date.

Complications induced by intravesicular instillation of BCG are relatively minor and self-limited; however, they can lead to rare and life-threatening complications that can be hard to diagnose, like small vessel vas-

culitis of the CNS.

The pathophysiology of BCGitis is not yet well understood. In previous studies it was thought to be a hypersensitivity reaction [3]. Others consider it to be a disseminated disease of *Mycobacterium bovis*.

The first case of small vessel vasculitis of the CNS induced by BCG was reported in 2018 [4] in a patient who developed limb weakness, aphasia, and loss of visual acuity. A brain MRI demonstrated multiple left-side hyperintense white matter lesions. He was diagnosed with primary CNS vasculitis after a brain biopsy was performed. After the resolution of neurological symptom under treatment he developed loss of acuity and underwent a right vitrectomy that came back positive for mycobacterium bovis. In a revision of the temporal lobe biopsy scant perivascular mycobacteria was revealed.

Our case demonstrated a similar cognitive decline and a brain MRI that showed neurovasculitis; however, our patient was only diagnosed after a positive bacteriol-

ogy result from a skin biopsy showing a disseminated systemic BCG infection resulting years after the last treatment.

The standard of treatment in BCGitis [5] is 2 months of isoniazid, rifampin, and ethambutol administered daily, followed by 7 months of isoniazid and rifampin. In case of meningitis, optimal duration of treatment lasts longer than 12 months. The tendency in systemic disease is to add steroids. Mortality rates are higher compared to mycobacterium tuberculosis and worse in patients diagnosed with human immunodeficiency virus. Mortality rates can also reach 16% when the vascular system is involved.

It is unfortunate that our patient did not get to be treated with the correct anti-mycobacteria therapy; nevertheless, he presented with a partial steroid responsive disease and the decrease in dosage lead to further deterioration.

Conclusions

BCG infection can be hard to diagnose; however, it should be considered when presented with systemic disease even if the symptoms manifest years after the last instillation.

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