Hemophagocytic Lymphohistiocytosis Following Systemic Bacillus Calmette-Guérin Infection: A Rare Complication of a Common Procedure

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We present a case of a 65-year-old woman diagnosed with papillary urothelial carcinoma and treated with intravesical bacillus Calmette-Guérin (BCG) instillations. The patient developed systemic BCG infection involving the liver and bone marrow (often referred to as BCGitis), complicated by hemophagocytic lymphohistiocytosis (HLH). Although BCGitis is a known adverse event, progression to HLH is rare, particularly in immunocompetent adults. Despite early recognition and escalation of therapy, including intravenous immunoglobulin (IVIG), corticosteroids, and an IL-1 antagonist, the prognosis remained poor, which was consistent with prior reports of high mortality in tuberculosis-associated HLH syndrome (TB-HLH). The diagnosis was microbiologically supported by GeneXpert Ultra, despite negative Ziehl-Neelsen staining and culture, underscoring the importance of molecular diagnostics in suspected BCG-related complications.

Intravesical BCG instillation remains a first-line treatment for superficial non-muscle-invasive bladder cancer. BCG activates the local immune response, leading to tumor cell death, with high efficacy and good tolerance [1].

HLH, a hyperinflammatory syndrome characterized by excessive macrophage activation and tissue inflammation and destruction, may be inherited in an autosomal recessive manner and typically presents in children. It may also be secondary to other conditions, such as hematologic malignancies, autoimmune disorders, or infections. TB-HLH is described in the literature and carries a poor prognosis, with mortality rates of up to 50% [2]. However, secondary HLH after intravesical BCG instillation is an infrequent clinical entity, with only a few cases reported to date [1]. Most previously described cases occurred in immunocompromised children or young adults with genetic mutations, such as severe combined immunodeficiency or interleukin-12 deficiency.

Although there are case reports of BCGitis as a late complication, our patient presented during bladder irrigation therapy [3]. This uncommon presentation required prompt diagnosis and rapid initiation of treatment, which could be challenging for those unaware of this rare complication.

PATIENT DESCRIPTION

A 65-year-old heavy-smoking female with a history of recurrent UTIs was diagnosed with a space-occupying lesion of the left bladder wall. TURB and biopsy revealed a papillary urothelial carcinoma, predominantly low grade, invading the subepithelial connective tissue. In addition, small, superficial foci (~2 mm in diameter) of high-grade urothelial carcinoma were also observed. The patient began bladder irrigation with BCG. Follow-up cystoscopies were clear.

Following her last bladder irrigation, the patient arrived at the emergency department (ED) complaining of lower abdominal discomfort without fever or other complaints. Her vital signs, physical examination, and blood samples were unremarkable except for leukopenia (2100 cells/microL). She was discharged home and returned the following day with a high-grade fever of 38.2°C, tachycardia of 112 bpm, profuse sweating, and jaundice.

A physical exam revealed a distended, tender abdomen, and

conjunctival jaundice. Her blood samples were notable for a normal complete blood count, mild neutrophilia, hyperbilirubinemia (total 6.48 mg/dl, direct 5.36 mg/dl), mildly elevated liver enzymes (hepatocellular and cholestatic), and markedly elevated C-reactive protein (CRP) (306 mg/L). Urine dipstick was positive for leukocytes, nitrates, and blood. A urology consultant recommended considering BCGitis and placing the patient under observation for the next 2 days. Piperacillin-tazobactam (4.5 g three times daily) was initiated. Blood and urine cultures were negative. The patient was eventually discharged home to complete a 7-day course of antibiotics.

One week after completing treatment, the patient returned to the ED with a high-grade fever (40°C) and asthenia. Her physical exam was unremarkable. The urine dipstick was positive for leukocytes and nitrates. Her blood samples showed leukopenia (2900 cells/microL), hyperbilirubinemia (3.57 mg/dl, direct 1 mg/dl), elevated liver enzymes, and a moderate decrease in CRP (182 mg/L). With a presumptive diagnosis of BCGitis, the patient was admitted to the internal medicine ward and received isoniazid, rifampin, ethambutol, and amikacin.

Over the following days, her hyperbilirubinemia worsened. Isoniazid was discontinued. An abdominal ultrasound showed no pathology except grade 2 fatty liver. She continued to deteriorate, with persistent pyrexia, worsening hypoxia and oxygen necessity, worsening pancytopenia, elevated liver enzymes, and no change in bilirubin or CRP. Additional blood samples showed elevated triglycerides (316 mg/dl), ferritin (160 ng/ml, later increasing to 4500 ng/ml), and soluble IL-2 (8492 U/ml).

A bone marrow and liver biopsy were performed while the patient continued to deteriorate. A liver biopsy showed a few non-necrotizing granulomas with giant polymorphonuclear cells. A Ziehl-Neelsen stain was negative. The bone marrow biopsy did not show granulomas; however, it revealed an increased number of histocytes in clusters and individually throughout the marrow. The findings of both biopsies suggested hemophagocytic syndrome. Notably, the bone marrow gene-expert ultra was positive for TB-complex (Trace).

In a multidisciplinary meeting, the HLH diagnosis was confirmed based on fulfillment of the HLH-2004 diagnostic criteria (pancytopenia, hypertriglyceridemia, hemophagocytosis on bone marrow biopsy, elevated ferritin, and elevated soluble IL-2). Treatment with dexamethasone and IVIG was initiated per standard guidelines, followed by anti-IL-1 after consulting with external experts. The patient was transferred to the intensive care unit, where she required renal replacement therapy. The patient improved hemodynamically and showed increases in all three cell lines; however, she remained in critical condition. She was lethargic, and there was no change in ferritin levels, kidney function, or liver enzymes. Two weeks after completing HLH treatment, the patient was transferred to another facility at the family's request, where she died without a change in therapeutic approach.

COMMENT

Short-term complications of intravesical BCG instillations are common, occurring in 75.5% of cases. These complications are typically local and self-limiting, including fever, malaise, and bladder irritation from cystitis. However, more severe local or systemic complications requiring medical attention occur at a lower rate of 2.35% [4]. Severe adverse reactions with systemic symptoms, often called BCGitis, are far less common and account for less than 5% of cases [1].

Moreover, a definitive diagnosis of BCGitis may be challenging, as the sensitivities of acid-fast staining, mycobacterial culture, and molecular testing are low, at 25.3%, 40.9%, and 41.8%, respectively. Prompt therapy with anti-tuberculosis treatment in addition to corticosteroids should be initiated with clinical suspicion of BCGitis, as the mortality of patients with disseminated BCG infection is 9.9%. In addition, 7.4% of patients present with long-term complications [5].

Our case highlights a rare but life-threatening complication of intravesical BCG instillation: secondary HLH. Although BCGitis is a known adverse event, progression to HLH is exceptional, particularly in immunocompetent adults. Our patient met diagnostic criteria for HLH, including persistent fever, cytopenias, hyperferritinemia, and elevated soluble IL-2 receptor levels. Despite early recognition and escalation of therapy, including IVIG, corticosteroids, and IL-1 blockade, the prognosis remained poor, which is consistent with prior reports of high mortality in TB-associated HLH.

Notably, the diagnosis was microbiologically supported by GeneXpert Ultra despite negative Ziehl-Neelsen staining and culture, underscoring the importance of molecular diagnostics in suspected BCG-related complications. Given the diagnostic challenge, early suspicion and multidisciplinary management are essential.

This case contributes to the limited body of literature on BCG-induced HLH and underscores the need for heightened awareness, particularly in patients with atypical post-BCG presentations.

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Let me never fall into the vulgar mistake of dreaming that I am persecuted whenever I am contradicted.
Ralph Waldo Emerson (1803–1882), American essayist, lecturer and poet, and champion of individualism

Capsule

The mutational landscape of STING-induced immunity

The STING (Stimulator of Interferon Genes) pathway is a central regulator of innate immunity, linking cytosolic DNA sensing to type I interferon production and inflammatory responses. Although STING has emerged as an important therapeutic target in infectious diseases, cancer, and autoinflammatory disorders, the functional effects of most naturally occurring or engineered STING mutations have remained poorly understood. **Zhang** et al. developed a massively parallel mutational assay to systematically evaluate thousands of STING variants, generating the first comprehensive sequence-function map of the human STING protein. The study identified amino acid residues that either enhance or suppress STING signaling and revealed distinct structural regions controlling ligand binding, protein stability, activation, and downstream interferon responses.

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Capsule

Toward conversational artificial intelligence for disease management

Current medical artificial intelligence (AI) systems perform well in isolated consultations but struggle with longitudinal patient care. **Liévin** and co-authors extended the AMIE (Articulate Medical Intelligence Explorer) platform to support continuous disease management across multiple patient encounters. The upgraded system integrates previous clinical encounters, longitudinal patient histories, laboratory data, and large collections of clinical practice guidelines while maintaining natural physician-patient conversations. Rather than simply answering isolated questions, the AI continuously updates diagnostic reasoning and therapeutic recommendations over time. In head-to-head evaluations involving complex longitudinal clinical cases, AMIE demonstrated superior disease management reasoning compared with experienced primary care physicians. The system excelled in identifying disease progression, recommending appropriate follow-up testing, adjusting therapies, and maintaining guideline adherence throughout repeated visits.

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