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Disseminated BCGosis following Systemic Absorption of Mycobacterium Bovis

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A study in non-human primates proposed intravenous (IV) Bacillus Calmette Guerin (BCG) as a superior anti-tuberculosis vaccine to standard intramuscular delivery[1]. We previously presented a case of multi-organ failure[2] following intravesical BCG, given as an adjunctive therapy for bladder cancer. Herein, we outline an additional three cases of disseminated BCGosis post intravesical treatment. These cases raise grave concern for the potential of a disseminated hypersensitivity response in vulnerable individuals to IV BCG.

All four patients in our series were males, aged 55-88 years. All patients received intravesical BCG as adjunctive therapy post trans-urethral resection of transitional cell carcinoma of the bladder and had previously received a number of BCG instillations. Patients presented with fever, malaise, and anorexia within two weeks of BCG instillation. Laboratory investigations revealed lymphopenia, with or without thrombocytopenia, and cholestatic pattern of liver function test (LFT) derangement. Routine microbiological cultures of sputum, urine and blood did not grow any organisms, and in particular mycobacterium tuberculosis was not cultured. Computed tomography of the thorax revealed widespread pulmonary nodular infiltrates. Transbronchial biopsy showed non-caseating granulomatous inflammation with giant cells in one patient. Another patient with significant LFT derangement underwent ultrasound guided liver biopsy showing granulomatous hepatitis and cholangitis. All patients initially continued to deteriorate despite standard antibacterial and supportive therapy. Clinical diagnosis of BCGosis was established based on persistent clinical suspicion and absence of other infectious aetiology. This was supported by histopathological findings in two of four patients. Once the diagnosis was confirmed, patients commenced standard anti-mycobacterial therapy consisting of Rifampicin, Isoniazid and Ethambutol. However, in one case the patient was commenced on Moxifloxacin, Ethambutol and Streptomycin due to elevated LFTs to avoid further hepatoxicity, and then transitioned to standard therapy once LFTs normalised. All patients were also commenced on tapering Prednisolone to achieve quiescence.

These cases highlight the potential deleterious effects that may occur when inactivated BCG gains access to systemic circulation. We postulate BCG gains access to systemic circulation via the diseased bladder, leading to systemic infection and a hypersensitivity syndrome. Interestingly, previous cases series have shown positive mycobacterial (BCG/M Bovis) samples are found outside the genitourinary tract in less than 50% of cases, whereas evidence of granulomatous inflammation is found in 86% of cases[3].

These findings are in keeping with our patient cohort where the predominant issue was a hypersensitivity granulomatous inflammatory response, as opposed to a diffuse infectious process. BCG can also cause disease outside pulmonary, hepatic, and genitourinary sites, a recent case report described the first known case of rhomboencephalitis attributed to disseminated BCG infection[4].

This report demonstrates that systemic absorption of BCG can lead to severe systemic symptoms. This sounds a stark note of caution for the development of intravenous BCG vaccination beyond non-human primates. While this route has afforded a better vaccine protection against tuberculosis in this model, it also seems likely that the administration of BCG by vein will also drive systemic immune processes in humans. Our finding in this case series, of a damaging inflammatory disease following systemic absorption of BCG, therefore introduces a significant consideration in the feasibility of developing parenteral BCG vaccination beyond primate studies.

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