Fatal Systemic Reaction After Multiple Doses of Intravesical Bacillus Calmette-Guérin for Polyposis

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OBJECTIVE: To report a case of fatal systemic reaction after intravesical administrations of bacillus Calmette-Guérin (BCG) for polyposis.

CASE SUMMARY: A 72-year-old white man was treated by monthly injections of intravesical BCG immunotherapy for polyposis of the urinary bladder. He received a total of eight injections; four hours after the seventh injection, he presented with pyrexia associated with chills, sweating, headache, and vomiting, which quickly resolved. Four hours after the eighth injection, the patient presented with the same symptoms plus a left-hemisphere deficiency. Results of a cerebral scan performed at this time were normal. The clinical status of the patient quickly worsened, with the appearance of disseminated intravascular coagulation, acute anuric renal insufficiency, rhabdomyolysis, hemolysis, and cytolytic and cholestatic hepatitis. The patient required hemodialysis and symptomatic treatment. Lactic acidosis with hemolytic–uremic syndrome appeared, and he died as the result of a multivisceral (respiratory, renal, hepatic) deficiency.

DISCUSSION: The patient presented with symptoms compatible with a severe systemic reaction to BCG therapy, a rare but possible adverse effect.

CONCLUSIONS: BCG instillation is a valuable tool in the therapy of bladder carcinoma, but increasing reports of severe adverse reactions should continue to remind practicing urologists to be alert to the possibility of common and uncommon reactions after its use.

KEY WORDS: BCG, fatal outcome, systemic reaction, intravesical.

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The instillation of bacillus Calmette-Guérin (BCG) into the bladder is an established treatment of recurrent low-grade bladder carcinoma.[1] Mild adverse effects such as malaise and a transient flu-like illness are commonly associated with this therapy.[2,3] More serious complications occur occasionally as a result of specific systemic infection such as pneumonitis, hepatitis, rhabdomyolysis, or acute renal failure. However, lethal reaction to BCG therapy, typically hemodynamic shock and disseminated intravascular coagulation, remains exceptional, despite some cases reported in the literature.[4,5] Additional cases of shock and disseminated intravascular coagulation have also been published,[6-9] but in these latter cases, the outcome was favorable, with or without antitubercular therapy.

We report the case of a 72-year-old man treated with monthly injections of in situ BCG immunotherapy for a benign polyposis of the urinary bladder, which is not a documented indication for this therapy. This patient developed an unusual and lethal hemolytic uremic syndrome during the treatment.

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CASE REPORT

A 72-year-old white man was diagnosed with a polyposis of the bladder in April 1996. In the past, the patient had no pathologies, such as tuberculosis, that could indicate that he was susceptible to BCG therapy complications. He received a total of eight monthly intravesical injections of BCG. The first six instillations were uneventful. Four hours after the seventh instillation, he developed a fever (value not reported) associated with chills, sweating, headache, and vomiting, all of which resolved spontaneously. Three weeks later, a subcutaneous injection of influenza virus vaccine and tetanus vaccine, administered as a preventive inoculation, was well tolerated. The patient did not receive other medications such as steroids or immunosuppressants. BCG instillations were not administered with prophylactic antibiotics, and no routine urine cultures were performed before each administration. Four hours after the eighth BCG instillation, the patient presented with the same symptoms as before; additionally, a left-hemisphere transient hemiparesis was noted. Results of a computed tomography were normal. In contrast to the previous episode, however, the patient's clinical status deteriorated dramatically. Within a few hours after the instillation, he developed disseminated intravascular coagulation (prothrombin 25%, decreased fibrinogen, thrombocytopenia [platelets $90 \times 10^3/mm^3$], D-dimerous 3000 µg/mL, positive fibrin degradation products 145 µg/mL), oliguria unresponsive to intravenous bumetanide 1 mg/h and alkalinization (serum creatinine 3.8 mg/dL, azotemia 1.56 g/L), rhabdomyolysis (creatine kinase >50 000 U/mL), intravascular hemolysis, and cytolytic and cholestatic hepatitis (aspartate transaminase 859 U/L, alanine transaminase 1192 U/L).

The acute renal failure required treatment with daily hemodialysis, which subsequently was substituted with continuous venovenous hemofiltration because of hemodynamic deterioration. Hemolytic uremic syndrome and thrombotic microangiopathy were recognized since the acute renal failure was associated with intravascular hemolysis, thrombocytopenia, and the presence of 6% schistocytes on the complete blood count, which decreased to 2% after plasmapheresis and administration of fresh frozen plasma. Seventeen days after the onset of these symptoms, the patient developed circulatory shock with lactic acidosis that failed to respond to the administration of vasoactive agents. In addition, he developed a persistent high-grade fever despite broad-spectrum antibiotic therapy (tazocillin, ofloxacin, vancomycin, amphotericin B). The patient died of multiorgan dysfunction syndrome (respiratory, renal, hepatic) 17 days after the first symptoms appeared. No autopsy was performed.

According to the Naranjo probability scale,[10] this adverse drug reaction was rated possible.

Discussion

Intravesical BCG immunotherapy is usually well tolerated, although 95% of patients experience minor adverse effects, usually a flu-like syndrome, which appears after the third injection and resolves spontaneously within 24 hours without specific treatment.[3] Serious complications have occasionally been reported, including hepatitis, renal abscesses, retroperitoneal lymphadenopathy, miliary pulmonary disease, and septic shock, all of which can be considered a systemic dissemination of BCG.[4] BCG therapy complications have been well studied in a large cohort of 2602 patients.[2] In this study, sepsis occurred in 0.4% of treated patients. The complication rate observed does not correlate with the strain of BCG used. The authors specified that complications of BCG vaccination in cancer therapy are relatively rare but are more frequent than in tuberculosis vaccination programs. Thus, while only one death per 50 million patients occurred when BCG was given for tuberculosis prophylaxis, a mortality rate of one death per 12 500 patients was observed when BCG was administered in the treatment of cancer patients.

Recommendations of these authors[2] concerning the treatment of complications are: (1) fever <38.5 ˚C: no treatment; (2) fever >38.5 ˚C for 12–24 hours and symptoms of allergic reactions (skin rash, arthralgia, migratory arthritis): isoniazid 300 mg/d for three months; (3) acute, severe visceral manifestations (granulomatous pneumonitis, hepatitis): isoniazid 300 mg/d, rifampin 600 mg/d, and ethambutol 1200 mg/d for six months; (4) severe sepsis complicated by circulatory shock, acute respiratory distress syndrome, and/or disseminated intravascular coagulopathy: isoniazid 300 mg/d, rifampin 600 mg/d, ethambutol 1200 mg/d plus cycloserine 500 mg twice a day, and an intravenous bolus of prednisolone 40 mg.

Specific disseminated sepsis is known to be the most severe complication following intravesical BCG instillation. In such cases, patients usually present with symptoms typical of sepsis, including circulatory shock, acute respiratory distress syndrome, and disseminated intravascular coagulopathy. Since the strain administered is a BCG-attenuated strain, triple or quadruple antituberculosis therapy is recommended. However, in severe cases, this therapy is often unsuccessful, and patients eventually die (Table 1).[4,5] Rawls et al.[5] reported five cases of sepsis following intravesical BCG that progressed to multiorgan failure and death in three patients despite administration of isoniazid, rifampin, and streptomycin. Postmortem examination revealed BCG organisms in the lung in only one patient (case 2). The two latter patients who had equally progressive sepsis survived with the use of cycloserine. Moreover, the bacteriologic cultures are often negative, perhaps due to the antitubercular treatment. However, in some patients, biopsy shows granuloma formations, which appear to be a hypersensitivity reaction since viable mycobacteria have not been recovered from these lesions. In these cases, treatment with steroids may be more advisable, but it is not easy to distinguish a priori a hypersensitivity reaction from a true mycobacterial infection. Thus, Baba et al.[8] reported a case of multiorgan failure, disseminated intravascular coagulation, and respiratory failure after administration of intravesical BCG. This is similar to our case, but the patient recovered with the administration of only antibiotics, not antituberculous therapy or corticosteroids.

The pathogenic mechanisms of the systemic reactions related to BCG therapy are complex: they involve either a systemic dissemination of the BCG-attenuated strain or an immune disorder (hypersensitivity reaction) with an important release of proinflammatory cytokines (interleukins, interferon, tumor necrosis factor, granulocyte-macrophage colony-stimulating factor). Sepsis results from the systemic absorption of BCG through the blood vessels of the inflamed or disrupted urothelium. For this reason, BCG should not be administered in the presence of cystitis or after a traumatic catheterization of the urinary tract. In our patient, BCG was not administered after a transurethral resection or cystoscopic examination, procedures that can play a role in the systemic dissemination of the bacillus (as in the case reported by Baba et al.[8]). However, after the seventh instillation, our patient developed a fever associated with chills, sweating, headache, and vomiting, which resolved spontaneously. According to the recommendations reported in the literature,[2] the BCG therapy should have been discontinued at this point. In some of the cases of BCG sepsis summarized in Table 1, patients experienced an episode of fever with previous instillations of BCG. The recommendations concerning BCG withdrawal are not always respected, and accurate guidelines must be provided to better inform physicians.

All cultures, especially the blood cultures, performed a few days after the patient was admitted to the hospital remained negative for mycobacteria two or three months later. In the course of the disease, the only positive culture was a pulmonary culture positive for *Candida tropicalis*, which was treated with amphotericin B. However, the first episode of fever after the seventh instillation, associated with the rapid onset of severe illness after the eighth instillation, made us believe that BCG therapy, rather than a fungal infection, was the cause of the complications devel-

Table 1. Cases of Fatal Sepsis Following Intravesical BCG Administration

Reference	Age (y)	Indication	Previous BCG Instillations (n)	BCG Cystitis	Antecedent Fever	Time Between BCG Therapy and Onset of Illness	Treatment of Illness	BCG-Related Death	Description of Illness	Postmortem Examination
Deresiewicz et al. (1990)[4]	67	bladder cancer	2			30 min; injection 3 made just after transurethral resection of prostate		yes; hypothermia, hypotension, disseminated mycobacterial infection	July 1987: fever, hypotension, anuria September 1987: urinary and fecal incontinence, weight loss of 4.5 kg, mental status markedly abnormal	disseminated mycobacterial infection centered about the genitourinary tract and retroperitoneum; kidney and lymph nodes positive for mycobacteria
Rawls et al. (1990)[5] case 1	70	bladder cancer	3	mild	severe (dose 2)	10 h after 4th injection	acetaminophen, isoniazid	yes (11 h after dose 4)	fever	
case 2	66	bladder cancer	6	mild	severe (dose 5); injection made after a traumatic catheterization	8 h; despite isoniazid prophylaxis	gram-negative antibiotics, isoniazid, rifampin	yes; intravascular coagulation, sepsis	fever, hemoptysis, lethargy, disseminated rash, diffuse intravascular coagulation, decreased fibrinogen and platelets	BCG organisms in the lung, chronic inflammatory infiltrates in liver and kidneys
case 3	63	bladder cancer	4	severe	none	96 h after dose 6	gram-negative antibiotics, isoniazid, rifampin, streptomycin	yes; multiorgan and acute respiratory failure	hypotension after dose 5; fever, hypotension, diffuse intravascular coagulation, sepsis after dose 6	granuloma formation with multinucleated giant cells in liver, bone, spleen, kidney
Present case	72	benign bladder polyposis	7	no	severe (dose 7)	4 h after 8th injection	diuretics, antibiotic therapy (ofloxacin, vancomycin, tazocillin, amphotericin B)	yes; multiorgan failure, hemolytic-uremic syndrome	fever, headache, vomiting, disseminated intravascular coagulation, anuric renal failure, rhabdomyolysis, hemolysis, cytolytic and cholestatic hepatitis	

BCG = bacillus Calmette-Guérin.

oped by our patient. Moreover, *C. tropicalis* sepsis is often associated with pustulous eruption,[11] especially observed in immunosuppressed patients; these conditions were not seen in our patient.

Antituberculosis therapy was not prescribed, as is usually recommended. The microangiopathy and the hemolytic uremic syndrome, which were considered hypersensitivity reactions, were instead treated with plasmapheresis and fresh frozen plasma. Broad-spectrum antibiotics including tazocillin, ofloxacin, and vancomycin were administered because of the suspicion of a superinfection and septic shock; however, this therapy failed to improve the patient's status and fever. Death occurred 17 days after the first symptoms appeared.

Summary

BCG therapy is considered to be a more effective treatment of superficial bladder tumors and in situ carcinoma than most chemotherapeutic agents, but the use of BCG therapy in benign bladder polyposis has not been reported. As illustrated by this case, BCG therapy may induce severe and sometimes lethal complications. Recommendations for the use of BCG therapy must be considered when the treatment regimen is developed[2] (in our case, the patient was treated for a benign polyposis), and the benefit/risk ratio should be assessed before beginning treatment. To our knowledge, the development of a hemolytic uremic syndrome following a reaction of hypersensitivity to BCG has not been previously described in the literature. This clinical feature occurring with this unusual indication for BCG therapy made this observation relevant. The recognition of risk factors, particularly a surgical manipulation of the genitourinary tract or concurrent cystitis favoring systemic BCG absorption, the appropriate treatment of adverse effects, the withdrawal of BCG instillations when warranted, and use of BCG for appropriate indications should significantly decrease the incidence of severe toxicity.

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EXTRACTO

OBJETIVO: Reportar una reacción fatal sistémica luego de la administración intravesicular del bacilo Calmette-Guérin (BCG) durante el tratamiento de una poliposis.

RESUMEN DEL CASO: Un hombre de 72 años fue tratado con inyecciones intravesiculares mensuales de BCG como inmunoterapia para poliposis de la vejiga urinaria. El paciente recibió un total de ocho inyecciones. Cuatro horas después de la séptima inyección presentó pirexia asociada con escalofríos, sudoración, dolor de cabeza, y vómito. En esa ocasión los síntomas se resolvieron rápidamente. Cuatro horas luego de la octava inyección, el paciente presentó los mismos síntomas y adiemás desarrolló una hemiparesis transitoria del lado izquierdo del cuerpo. Un rastreo tomográfico cerebral llevado a cabo en ese momento fue normal. El estado clínico del paciente se deterioró rápidamente, presentando un cuadro de coagulación intravascular diseminada, rabdomiolisis, hemolisis y hepatitis citolítica y colestática. El manejo del paciente requirió hemodialisis y tratamiento sintomático. Finalmente el paciente desarrolla acidosis láctica y un síndrome hemolítico-urémico que lo lleva a una deficiencia multiviceral (respiratoria, renal, hepatica) de la cual muere.

DISCUSIÓN: Todos los síntomas presentados por el paciente son compatibles con una reacción sistémica severa a uno terapia de BCG. Esta reacción ya ha sido previamente clasificada como posible, aunque tan infrecuente que se considera rara.

CONCLUSIONES: La instilación de BCG es una herramienta terapéutica valiosa en el tratamiento del carcinoma de la vejiga, pero el aumento en los reportes de efectos adversos debe continuar alertando a los urologos de la posibilidad de reacciones adversas a este producto.

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RÉSUMÉ

OBJECTIF: Décrire un cas de réaction systémique fatale à la suite d'administrations intravésicales de bacille de Calmette-Guérin (BCG) pour traiter une polypose.

RÉSUMÉ DU CAS: Un patient âgé de 72 ans était traité par des injections mensuelles de BCG intravésical pour une polypose. Il a reçu un total des huit injections. Quatre heures après la septième injection, le patient a présenté de la fièvre associée à des frissons, des sueurs, des céphalées, et des vomissements qui ont régressé rapidement. Quatre heures après la huitième injection, le patient a présenté les mêmes symptômes que précédemment associés à une hémiplégie gauche. Un scanner cérébral effectué à ce moment était normal. Rapidement, l'état clinique du patient s'est aggravé avec l'apparition d'une coagulation intravasculaire disséminée, d'une insuffisance rénale aiguë anurique, d'une rhabdomyolyse, d'une hémolyse, et d'une hépatite mixte. Le patient est alors traité par des séances d'hémodialyse et des traitements symptomatiques. Une acidose lactique sur un syndrome hémolytique et urémique vient aggraver la symptomatologie et le patient décède dans un tableau de déficience multiviscérale.

DISCUSSION: Tous les symptômes présentés par ce patient sont compatibles avec une réaction systémique sévère à la BCG thérapie, complication certe rare mais à diagnostiquer rapidement.

CONCLUSIONS: L'instillation de BCG est devenu un traitement standard de cancer de la vessie. Cependant, l'augmentation de la notification de complications sévères doit alerter les cliniciens sur la possibilité de survenue de réactions graves dans les suites de l'utilisation intravésicale de BCG.

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