

## BRIEF REPORT: MENINGITIS DUE TO IATROGENIC BCG INFECTION IN TWO IMMUNOCOMPROMISED CHILDREN

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**V**ACCINATION with bacille Calmette-Guérin (BCG), an attenuated strain of *Mycobacterium bovis*, has been used extensively throughout the world as immunoprophylaxis against tuberculosis. Since 1976, intravesical administration of BCG has been used to treat superficial transitional-cell carcinoma of the bladder.<sup>1</sup> In both uses the complications of therapy have been rare, and the majority of serious side effects have occurred in immunocompromised persons.<sup>2-5</sup>

In this report we describe two children with leukemia treated at our institution in whom BCG-associated meningitis developed. Neither child was receiving BCG as part of the immunotherapy for leukemia, and neither had a history of BCG vaccination. We speculate that both infections may have been caused by the accidental inoculation of BCG during the administration of intrathecal chemotherapy.

Although proof is lacking, we believe that the contamination occurred in or near the biologic-safety cabinet in the hospital pharmacy, where both the chemotherapeutic agents used to treat these patients and the BCG used to treat patients with bladder cancer were prepared.

### CASE REPORTS

#### Patient 1

A three-year-old girl with acute lymphoblastic leukemia was admitted to the hospital in October 1993 with meningitis. Leukemia had been diagnosed in January 1993, and the patient had been given standard treatment. By the time of her admission, she was in remission, receiving vincristine, prednisone, mercaptopurine, and oral methotrexate regularly, as well as intrathecal methotrexate every 84 days.

Two months before admission, the patient was treated with cephadrine for what appeared to be an infected insect bite on her lower back. The lesion resolved, but a tender mass developed nearby. The mass was incised and drained 19 days before the patient's admission. Drainage was required again one week later, with subsequent healing of the wound. Gram's staining and routine bacterial cultures of the drained material were negative.

The patient had had headaches two weeks before admission. The workup yielded a normal computed tomographic scan of the head and a normal chest radiograph. Lumbar puncture showed 59 white cells per cubic millimeter of cerebrospinal fluid, with 90 percent

mononuclear cells and 10 percent polymorphonuclear cells. The glucose concentration was 49 mg per deciliter (2.7 mmol per liter). Gram's staining and bacterial cultures of cerebrospinal fluid were negative.

On the day of admission, the laboratory reported that mycobacteria, subsequently identified as BCG, had grown from the culture of material previously drained from the patient's back lesion. By this time, the patient's headaches had worsened and fever had developed. She began receiving isoniazid, rifampin, streptomycin, and pyrazinamide. Skin testing with 5 units of purified protein derivative of tuberculin (PPD) produced no induration with positive candida and tetanus controls. Additional evaluation included magnetic resonance imaging (MRI) scans of the spine, abdomen, and pelvis, which were normal, and of the brain, which showed borderline ventricular enlargement.

Cultures of cerebrospinal fluid obtained at the time of the patient's admission to the hospital were positive for *M. tuberculosis* complex approximately three weeks after collection. When further testing identified the isolates as BCG resistant to pyrazinamide, ethionamide therapy was substituted, since it has excellent penetration into cerebrospinal fluid. After the patient's discharge from the hospital, her headaches and fevers gradually resolved. A lumbar puncture three months later showed some improvement, and mycobacterial cultures were negative. Treatment with streptomycin and ethionamide was discontinued after two months of therapy. The patient continued to take isoniazid and rifampin, completing a 12-month course. The chemotherapy for leukemia was continued without interruption.

The patient was born in southern California but had visited Colombia in 1990. She was not known to have been vaccinated with BCG, and there was no scar from such a vaccination. Her only contact with large animals had been a visit to a petting zoo, and she had never ingested raw milk. An investigation of her contacts was unrevealing, except for the fact that an uncle had received isoniazid for six months as preventive therapy in 1991.

#### Patient 2

Meningitis was diagnosed in a five-year-old boy in December 1993. He had been given a diagnosis of acute lymphoblastic leukemia in April 1991 and had been given standard treatment. He entered remission and was receiving maintenance chemotherapy that included vincristine, prednisone, mercaptopurine, and oral methotrexate, as well as intrathecal methotrexate administered every 84 days.

During a routine lumbar puncture three months before admission, the patient was noted to have a small midline pustule in the lower lumbar region. A bacterial wound culture was performed (and subsequently found to be negative), and the patient began receiving oral cephadrine therapy. The lesion resolved.

Two months later, his condition was evaluated after he had two weeks of headaches and rhinorrhea. Sinusitis was diagnosed, and he was treated with amoxicillin. Three weeks later, he was still having headaches, now with fever and moderate weight loss. A physical examination was unremarkable. The evaluation included a lumbar puncture, which showed 230 white cells per cubic millimeter of cerebrospinal fluid (67 percent mononuclear cells and 33 percent polymorphonuclear neutrophils). The protein concentration of the cerebrospinal fluid was 107 mg per deciliter, and the glucose concentration was 13 mg per deciliter (0.72 mmol per liter). Repeated studies of cerebrospinal fluid over the next two weeks remained persistently abnormal. Cultures and serologic tests for organisms other than mycobacteria were negative. No blasts were seen on cytologic examination of the cerebrospinal fluid. MRI of the head and chest roentgenography were normal. Skin testing by the Mantoux method showed no response to 5 units of PPD with a positive candida control.

About three weeks after incubation, cultures of the initial samples of cerebrospinal fluid grew mycobacteria that were subsequently identified as BCG. The patient was treated with isoniazid, rifampin, and pyrazinamide. Ten days later, streptomycin was added, and because of concern about possible BCG infection, ethionamide was substituted for pyrazinamide.

Within a month the patient showed marked clinical improvement. A follow-up lumbar puncture about three months later also showed improvement. He received streptomycin and ethionamide for

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2 months and continued to receive isoniazid and rifampin for a total of 12 months. His chemotherapy was not interrupted.

The patient was born in the United States, had not traveled outside the country, and had not been vaccinated with BCG. He had never ingested raw milk, and his only contact with large animals was with horses belonging to his grandfather. A contact investigation did not detect tuberculosis in the family. A Guatemalan housekeeper was unavailable for evaluation.

### METHODS

Specimens of cerebrospinal fluid from both children and the wound-drainage specimen from Patient 1 were cultured for mycobacteria by inoculation onto Lowenstein-Jensen medium and Wallenstein medium, and into Bactec 12B medium. Growth was noted in these cultures after an average of 22 days. The isolates were tested (Park Clinical Laboratories, Los Angeles) by a DNA-RNA probe assay (GenProbe, San Diego, Calif.) and found to belong to the *M. tuberculosis* complex. Niacin and nitrate-reduction tests of all the isolates were negative, and susceptibility studies showed resistance to pyrazinamide and susceptibility to streptomycin, isoniazid, ethionamide, rifampin, ethambutol, kanamycin, capreomycin, ciprofloxacin, ofloxacin, and amikacin. High-performance liquid chromatography (Park Clinical Laboratories) was used according to previously described methods to determine that the isolates were *M. bovis* BCG.<sup>6,7</sup> Patterns of large restriction fragments of genomic DNA were compared by pulsed-field gel electrophoresis as previously described.<sup>8</sup> After digestion with *Dra*I, *Xba*I, *Asn*I, and *Spe*I, large restriction fragments with identical patterns were seen for the isolates from all three cultures. The patterns matched those of the Connaught, Tice, and Australia strains of BCG obtained from the American Type Culture Collection and the strain obtained from the hospital pharmacy. They differed from 13 other BCG strains, including the Mexico, Pasteur, and Glaxo strains.<sup>9</sup>

### DISCUSSION

Complications of BCG vaccination are uncommon but have been well described. The reported estimates of risk depend in part on the population studied and on the strain of BCG used in the vaccine.<sup>2</sup> The Centers for Disease Control and Prevention recently stated that from 1 to 10 percent of vaccinated persons have some side effects, usually a local reaction, and that 1 to 10 deaths or cases of disseminated disease occur per 10 million doses administered.<sup>10</sup> Most of the serious complications of BCG use occur in immunocompromised persons. Complications have been documented among patients infected with the human immunodeficiency virus, but the precise risk associated with routine BCG vaccination among such patients has not been determined.<sup>11-15</sup>

In the United States, BCG is most widely used to treat superficial bladder cancer. The dose used for this purpose is considerably higher than that used in vaccination. Minor local reactions are not uncommon after intravesical administration.<sup>4</sup> More severe complications are rare and can include pneumonitis, hepatitis, abscess of the psoas muscle, and sepsis.<sup>16-19</sup>

Only a few cases of central nervous system infection due to BCG have been reported. BCG meningitis developed in three immunocompetent children five to six months after vaccination.<sup>20,21</sup> One child died, and two had favorable outcomes. In a case similar to those in this report, Coppes et al.<sup>22</sup> described a six-year-old Canadian girl with leukemia in whom a BCG-related

brain abscess and meningitis developed. No source of the BCG was identified. The child was treated with isoniazid and rifampin, and she recovered fully. In another report, a six-year-old child with leukemia in San Diego, California, had an epidural abscess of the lumbar spine due to *M. bovis* infection.<sup>23</sup> Like our patients, he underwent frequent lumbar punctures for the administration of intrathecal chemotherapy. Unfortunately, that report did not state whether further testing was performed to determine whether the isolate was BCG.

We have some concern that the frequency of BCG infection may be underestimated. This may be the case if laboratories do not routinely perform complete testing to determine the identity of mycobacterial isolates, thereby risking their misclassification as *M. tuberculosis*. In addition, in cases of mycobacterial meningitis, small volumes of cerebrospinal fluid may yield negative cultures, since the organisms are typically present in low concentrations.

In our patients, the source of the BCG remains a matter of some speculation. Community-acquired infection was thought to be unlikely, on the basis of the case histories and the negative tuberculin tests of household members. Since both patients had skin lesions in the area of previous lumbar punctures before the development of meningitis, we considered direct inoculation of BCG during these procedures the most likely mechanism of transmission.

At our hospital, BCG is used solely to treat bladder cancer. Before these cases, both BCG and intrathecal chemotherapeutic medications were prepared in the same pharmacy, in the same biologic-safety cabinet. Doses of BCG were prepared on most days, beginning at 7 a.m. On days when intrathecal methotrexate was ordered, the pharmacists began preparing it after 9 a.m., so that the dose would be ready by the time of the pediatric oncology appointments.

The intrathecal chemotherapy given to our patients may have been accidentally contaminated during the preparation of these products. This hypothesis is supported by the finding that the large restriction-fragment patterns of the isolates obtained from the patients matched those of the BCG from the hospital pharmacy. However, an intensive review of the techniques used by the pharmacy personnel to prepare BCG and methotrexate failed to identify any means by which contamination might have occurred. In addition, cultures of samples from the surfaces on which the products were prepared and those nearby, including the hood, failed to grow any mycobacteria. Five other children who received intrathecal medication during this period were followed closely, and none had skin lesions or evidence of meningitis.

We also conducted an informal survey of a number of other institutions where BCG is frequently used. They reported no similar cases, and their methods of preparing and handling BCG, especially in relation to other medications prepared concurrently (including

chemotherapeutic agents), did not differ substantially from ours (Switzky H: personal communication).

Despite the lack of proof, we must consider that the common perception of BCG as a chemotherapeutic agent rather than a biologic and potentially infectious one contributed to the iatrogenic transmission of the organism in these two cases. As a precautionary measure, we have changed the practice in our pharmacy, dedicating one biologic-safety cabinet solely to the preparation of BCG and preparing chemotherapeutic agents for administration in a separate pharmacy. Although the present guidelines do not mandate such measures, it may be prudent for other institutions to review their practices and change their protocols as indicated.

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