Disseminated Bacille Calmette-Guérin Disease After Vaccination: Case Report and Review

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The attenuated bacille Calmette-Guérin (BCG) vaccine is administered to prevent tuberculosis. Complications of vaccination are uncommon. We report a new case of disseminated BCG disease and review 27 additional cases identified from a review of >5,000 reports published between 1980 and 1996. Twenty-four of the 28 total cases were associated with an immune deficiency, including nine cases of AIDS. Seventy-one percent of the cases occurred in children younger than 2 years old. Sixty-eight percent of the patients were male. About one-half of the patients were vaccinated in a developed nation, but 85% of the cases were reported from a developed nation. Response to therapy was poor, with an overall mortality rate of 71%. We made two new observations. Disseminated BCG disease has historically been a disease of infants, but cases now occur in adults and older children coinfected with human immunodeficiency virus. Cases also occur after revaccination of individuals who were anergic following the initial administration of BCG vaccine. Disseminated BCG disease is an uncommon but devastating complication of vaccination that should be considered in the appropriate clinical setting. Immunocompromised infants and patients with late-stage AIDS are at greatest risk and respond poorly to standard therapies.

The original BCG strain of Mycobacterium bovis was derived from multiple passages of wild-type M. bovis [1]. BCG vaccine is administered worldwide to prevent tuberculosis and is considered to have an excellent safety profile. However, complications do occur, including abscesses at the site of inoculation and localized lesions such as osteitis [2]. The most serious complication is disseminated disease.

We report a new case of disseminated BCG disease in an infant with immunodeficiency. We also present a working definition of disseminated BCG disease, which we use to review the literature on disseminated BCG disease resulting from vaccination. We identified 28 definite [3–21] and nine probable [22–28] cases reported from 1980 through 1995, a period that overlaps minimally with those of a previous retrospective review [29] and a prior prospective study [30]. The topic of disseminated BCG disease warrants reevaluation, given improved diagnostic methods, an expanded concept of disseminated mycobacterial disease, and the progression of the AIDS epidemic.

Case Report

An 8-month-old girl presented to a pediatric hospital in Vitoria, Brazil, with a 3-week history of bloody diarrhea, cough, and fever; her family history was unavailable. Her medical history revealed that she had had frequent illnesses since birth, including bronchiolitis, pneumonia, and chronic bloody diarrhea. Immunization over the right deltoid muscle with Moreau BCG vaccine (Fundao Ataufo de Paiva, Rio de Janeiro) at 10 days of age had resulted in a nonhealing ulcer. One month before admission, the child developed dyspnea, productive cough, abdominal distention, increased diarrhea, fever, and an enlarging right axillary mass.

At the time of admission, the child had a temperature of 38.9°C and labored breathing. She appeared pale and listless and had moderate thrust. The site of BCG vaccination was enlarged, erythematous, and weeping. A soft, mobile right axillary lymph node (5 cm in size) was present. There were diffuse rhonchi. Abdominal examination showed distention, hepatosplenomegaly, and a firm, mobile 3-cm mass in the epigastrium.

Laboratory studies at the time of admission revealed a WBC count of 12,700/mm³ (10% lymphocytes), hematocrit of 17%, and platelet count of 118,000/mm³. Testing for antibody to HIV by ELISA was negative twice. Ultrasonography confirmed the presence of a heterogeneous abdominal mass measuring 3.0 × 6.2 cm.

A tuberculin test was nonreactive, and microscopic examinations of sputum and gastric aspirates were negative for acid-fast bacilli. However, biopsies of the axillary and abdominal masses yielded lymph tissue that was 3+ positive for acid-fast organisms. A presumptive diagnosis of disseminated tuberculosis was made, and therapy with isoniazid, rifampin, and pyrazinamide was begun. The infant remained febrile, developed progressive leukopenia and hypoxemia, and died on the 29th day of therapy. Necropsy showed pulmonary Pneumocystis
carinii infection, esophageal candidiasis, and diffuse lymphadenopathy. Well-developed granulomas and many acid-fast bacilli were found in both the liver and spleen.

Methods

Culture and identification. The biopsy sample from the abdominal mass was cultured, and the isolate was identified to the species level by growth inhibition by p-nitroacetylaminohydroxypropionophenone and thiophene-2-carboxylic acid hydrazide, nitrate reduction, and niacin production. Drug susceptibility testing was performed by means of the BACTEC System (Becton Dickinson, Sparks, MD). Two additional methods were used to confirm the identity of the isolate as BCG. A specific genomic region containing the major polymorphic tandem repeat (MPTR) was amplified by PCR analysis, and restriction enzyme analysis (REA) was carried out according to the published method [31]. HPLC was performed by the Centers for Disease Control and Prevention as previously described [32].

Literature search and case classification. We conducted a literature search by using MEDLINE with the subject heading terms Mycobacterium bovis BCG, BCG vaccine, and bacillus Calmette-Guerin and the text words BCG, Calmette, and Guérin. We limited our search to the English- and French-language literature from 1980 through 1995. We also conducted a literature search by using the Latin American and Caribbean Health Sciences Literature of the Pan-American Health Organization Library with use of a similar search strategy. These databases include literature published since 1985. Reference lists of case reports, trials, and reviews were also examined for relevant articles.

Cases resulting from any mechanism other than vaccination (e.g., intravesical instillation of BCG for the treatment of bladder cancer) were excluded from analysis. Cases identified by the literature searches were classified according to table 1. Each potential case of disseminated disease was then evaluated according to the working definition shown in table 2. The rationale for this definition is presented under Discussion.

Results

Case. The isolate from the abdominal mass in our patient was identified as BCG by the methods described above [31–33]. The isolate was susceptible to isoniazid, rifampin, streptomycin, and ethambutol and was resistant to pyrazinamide. Our case was classified as definite disseminated disease on the basis of evidence of infection at three extraregional sites (abdominal lymph node, liver, and spleen) and a systemic syndrome consistent with mycobacterial disease (fever, weight loss, anemia, and death).

Literature review and case classification. We reviewed >5,000 reports and identified 27 additional cases of definite disseminated BCG disease that were reported from 1980 through 1995; these cases are summarized in table 3. Seventy-one percent (20) of 28 cases occurred in patients younger than 2 years of age. Four cases occurred in adults. Sixty-eight percent of patients for whom sex was reported were male. Eighty-six percent (24) of 28 cases occurred in immunocompromised hosts. AIDS was identified in 32% of all cases. Other immunodeficiencies included severe combined immunodeficiency (five patients), chronic granulomatous disease (three), and unidentified cell-mediated immune defects (seven).

Sites of dissemination were established by culture or histological demonstration of acid-fast bacilli. The most common sites of dissemination were lymph nodes, which were identified in 24 of 28 cases. Blood or bone marrow was positive for BCG in nine cases. Other common sites of dissemination were the lung, liver, spleen, skin, and bone.

The most commonly reported symptoms in the definite cases of disseminated BCG disease were fever, lymphadenopathy, and weight loss. Failure to thrive and hepatosplenomegaly were also common. Reporting of symptoms was incomplete, and associating symptoms with disseminated BCG disease was sometimes difficult because of comorbid illnesses.

Table 1. Classification of complications following BCG vaccination.

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>Regional disease</td>
<td>Persistent ulcer, abscess, fistula, or lymphadenopathy limited to the region of inoculation.</td>
</tr>
<tr>
<td>Extra-regional localized disease</td>
<td>Infection of a single anatomic site, such as osteitis or cutaneous abscess, outside the region of inoculation.</td>
</tr>
<tr>
<td>Disseminated disease</td>
<td>See detailed definition in table 2.</td>
</tr>
<tr>
<td>Other BCG syndromes</td>
<td>Syndromes following vaccination in which bacteria are not identified, such as keloid formation and uveitis. These syndromes may have an immune basis.</td>
</tr>
</tbody>
</table>

NOTE. Data are adapted from [30].
Table 2. Working definition of disseminated BCG disease.

Cases were defined as definite disseminated BCG disease when all three of the following conditions were met:
1. BCG cultured and identified by biochemical methods at least.
2. Dissemination evidenced by either A or B.
   A. A positive blood or bone marrow culture.
   B. Evidence of infection at two or more anatomic sites beyond the region of vaccination. Evidence of infection includes a positive culture or histopathologic demonstration of acid-fast bacilli.
3. A systemic syndrome compatible with mycobacterial disease. Typical manifestations include fever, weight loss, anemia, and death.

Discussion

Background. The original BCG strain was derived from *M. bovis* and was first used as a tuberculosis vaccine in 1921. Over 3 billion doses of BCG vaccine have been given since 1948, and it has been considered to be safe [1]. However, complications do occur. Lotte et al. [29] reviewed >1,000 reports and found that 10,000 complications of BCG vaccination were reported between 1921 and 1982. Their retrospective review identified 60 cases of dissemination for which the mortality rate was 50%. In a later prospective survey of complications of BCG vaccination [30], the same researchers studied all infants vaccinated between 1979 and 1981 in six European countries. The 5.5 million infants who were vaccinated were followed up through 1983 by means of a questionnaire. The estimated incidence of disseminated disease was 2 cases per 1 million vaccinated children, and the mortality rate was 80%.

BCG disease and immunodeficiencies. Serious complications of BCG vaccination, such as generalized lymphadenitis [34] and disseminated disease [35], do occur in normal hosts, but these complications are exceptional. In the retrospective review of disseminated BCG disease by Lotte et al. [29], cellular immunodeficiency was identified as the chief risk factor for fatal outcome. Of the 60 total patients who were identified, 31 died. All patients who died had a “definite” or “highly probable” cellular immunodeficiency. Twenty-nine patients recovered. Eleven of these 29 patients also had a “partial” or “serious” immune defect.

Our literature review confirms a predilection of disseminated BCG disease in immunocompromised hosts. Immune defects were identified in 24 of the 28 definite cases. Of the 20 patients who died of disseminated BCG disease, all had an immune defect. In contrast, of the eight patients who recovered, only four had an identified immunodeficiency.

BCG disease and HIV infection. There have been many reports of local complications of BCG vaccination in patients with HIV infection, especially abscesses, adenitis, and fistulae. These local complications of BCG vaccination have occurred in patients with both symptomatic and asymptomatic HIV infection [36–41].

Symptomatic HIV-infected patients who are immunized with BCG vaccine have developed the devastating complication of disseminated disease (cases 9 and 30). Whether asymptomatic HIV-infected patients who are immunized with BCG vaccine are at increased risk for disseminated disease is more controversial. There have been reports suggesting that this is true [42]; cases 1, 6, 7, and 31 also suggest that asymptomatic HIV-infected patients who are immunized with BCG vaccine are at increased risk. There has even been one case of apparent reactivation of BCG disease and symptomatic dissemination that occurred in a patient with AIDS 30 years after vaccination (case 4); this case suggests that HIV-infected patients can develop complications of BCG vaccination even if they are immunized with BCG vaccine before the acquisition of HIV infection.

Not all cases of disseminated BCG disease in HIV-infected patients are reported. BCG vaccination is currently used where HIV infection is epidemic but testing for HIV infection is not routinely done. In the developing nations, lack of resources makes the routine and accurate identification of pathogens in patients with AIDS difficult. Disseminated BCG disease may be misdiagnosed as infection due to *Mycobacterium tuberculosis* or *M. bovis*. The relative paucity of cases in the developing world that were identified by our review and that of Lotte et al. [29] may reflect incomplete reporting or reporting in sources not accessed by our search strategies.

There have been prospective studies identifying the risk of disseminated disease in asymptomatic HIV-infected patients [4, 43–47]. One recent study [48] enrolled 155 adults with AIDS who had received BCG vaccination as children. Blood specimens for mycobacterial cultures were obtained at study entry and at 6 months. None of the cultures of specimens from these patients were positive for BCG. Most studies are small with inadequate follow-up; therefore, the actual risk to asymptomatic HIV-infected patients remains poorly characterized.

Identification of BCG. Mycobacterial isolates are frequently identified in clinical microbiology laboratories to the level of the *M. tuberculosis* complex, which includes *M. tuberculosis*, *M. bovis*, *Mycobacterium africanum*, and *Mycobacterium microti*. Suspicion that an *M. tuberculosis* complex isolate may be BCG is often based on the clinical history (especially the temporal relationship between vaccination and disease) or the presence of disease in the region of vaccination. The combi-
nation of biochemical and growth features can strongly suggest that an isolate is BCG, but none of these features are definitive [49, 50].

There are four validated methods for the definitive identification of BCG. These four methods are phage typing [51], HPLC [52], restriction fragment length polymorphism analysis with use of the insertion element IS1081 as a probe (i.e., IS1081 fingerprinting) [53], and amplification of a specific region containing the MPTR by PCR followed by REA [31]. Each of these methods has advantages and disadvantages. Phage typing is laborious and not widely available. HPLC is rapid and easy to perform, but it requires a fresh isolate on proper medium as well as specialized and expensive equipment. IS1081 fingerprinting is more laborious, requiring careful isolation of DNA from a large bacterial culture followed by Southern blot hybridization with a specific probe. This technique is generally not available to clinical microbiology laboratories. Amplification of MPTR by PCR and REA only requires a small specimen that an isolate is BCG, but none of these features are definitive [31], and may be directly applicable to smear-positive clinical specimens, as has been reported for other PCR-based methods for strain differentiation [54].

**Rationale for the working definition of disseminated BCG disease.** The working definition of disseminated BCG disease
Ethiopia/Israel; and kidneys. Organisms were found up to 3 years after vaccination; and dissemination by either a causes; histological examination of tissues demonstrated granu-

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Country: patient/report</th>
<th>Age/sex</th>
<th>Immune defect</th>
<th>Confirmed site(s) of dissemination</th>
<th>Systemic syndrome</th>
<th>Antimicrobial therapy</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>29 [22]</td>
<td>Ethiopia/Israel</td>
<td>3 mo/F</td>
<td>AIDS</td>
<td>R LN</td>
<td>Fever, failure to thrive, HSM, anemia</td>
<td>INH, Rif, Stm</td>
<td>Died</td>
</tr>
<tr>
<td>30 [23]</td>
<td>Algeria/France</td>
<td>32 y/M</td>
<td>AIDS</td>
<td>R LN</td>
<td>Fever, weight loss, diarrhea, SM</td>
<td>INH, Rif, Eth, PZA</td>
<td>Died</td>
</tr>
<tr>
<td>31 [24]</td>
<td>Haiti/France</td>
<td>4 mo/M</td>
<td>AIDS</td>
<td>NR</td>
<td>Failure to thrive, LAD, HSM</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>32 [25]</td>
<td>Saudi Arabia/Saudi Arabia</td>
<td>9 mo/F</td>
<td>SCID</td>
<td>Skin, multiple bone sites</td>
<td>Fever, failure to thrive, diarrhea</td>
<td>NR</td>
<td>Died</td>
</tr>
<tr>
<td>33 [13]</td>
<td>Chile/Chile</td>
<td>5 mo/M</td>
<td>CGD</td>
<td>D LN</td>
<td>NR</td>
<td>INH, Rif, Stm</td>
<td>Died</td>
</tr>
<tr>
<td>34 [26]</td>
<td>South Africa/South Africa</td>
<td>4 mo/M</td>
<td>CGD</td>
<td>D LN</td>
<td>Failure to thrive, HSM, LAD</td>
<td>INH, Rif, Eth, PZA</td>
<td>Died</td>
</tr>
<tr>
<td>35 [13]</td>
<td>Chile/Chile</td>
<td>10 mo/M</td>
<td>CMI</td>
<td>D LN</td>
<td>NR</td>
<td>INH, Rif, Amik</td>
<td>Survived</td>
</tr>
<tr>
<td>36 [27]</td>
<td>France/United Kingdom</td>
<td>1 y/F</td>
<td>Transient</td>
<td>D LN</td>
<td>Fever, weight loss, LAD</td>
<td>INH, Eth, Stm, Clof</td>
<td>Died</td>
</tr>
<tr>
<td>37 [28]</td>
<td>United Kingdom/United Kingdom</td>
<td>4 mo/F</td>
<td>Omenn’s disease</td>
<td>Thigh abscess (at vaccination site)</td>
<td>Fever, failure to thrive, LAD</td>
<td>INH, Rif, Amik</td>
<td>Survived</td>
</tr>
</tbody>
</table>

NOTE. Amik = amikacin; CGD = chronic granulomatous disease; Clof = clofazimine; CMI = cell-mediated immune defect; D = distant; Eth = ethambutol; Ethi = ethionamide; HSM = hepatosplenomegaly; INH = isoniazid; LAD = lymphadenopathy; LN = lymph node; NR = not reported; PZA = pyrazinamide; R = regional; Rif = rifampin; SCID = severe combined immunodeficiency; SM = splenomegaly; Stm = streptomycin.

(table 2) requires the following: a culture positive for BCG (the identification of which has been confirmed by biochemical methods at least); demonstration of dissemination by either a positive blood or bone marrow culture or evidence of infection at two or more anatomic sites beyond the region of vaccination; and signs and symptoms consistent with mycobacterial disease. This working definition was developed before our literature search as a tool to identify only definite cases. We used the literature on disseminated Mycobacterium avium complex disease [55] and other disseminated mycobacterial diseases [56] to develop the working definition of disseminated BCG disease.

Some researchers have used the terms disseminated or generalized to refer to any locus of infection beyond the region of vaccination. We believe that there are important distinctions between extraregional localized disease (e.g., isolated osteitis or lymphadenitis) and disseminated disease involving multiple organ systems. For example, disseminated BCG disease occurs almost exclusively in immunocompromised hosts, is frequently associated with a negative tuberculin test, is not associated with histological findings of well-formed granulomas [57], responds poorly to therapy, and is frequently fatal. In contrast, generalized BCG lymphadenitis occurs in immunocompetent hosts (for whom results of tuberculin tests are normal), provokes a typical histological response [58, 59], and can sometimes resolve without therapy [34].

The third requirement for our working definition is a systemic syndrome consistent with mycobacterial disease. This requirement is intended to distinguish disseminated BCG disease from the asymptomatic dissemination of BCG that occurs after vaccination of infants with an intact immune system. In fact, dissemination of BCG is a normal sequela of BCG vaccination [60]. In 1956, Gormsen [61] performed autopsies on BCG-vaccinated infants and children who died of unrelated causes; histological examination of tissues demonstrated granulomas in many distant organs, including liver, lungs, spleen, and kidneys. Organisms were found up to 3 years after vaccination without evidence of clinical disease. This work was effectively reproduced by Trevenen and Pagnostik [62] in 1982.

Treatment of disseminated BCG disease. There is pessimism in the historic literature regarding the treatment of disseminated BCG disease in immunocompromised hosts. In 1972, Sicevic [63] wrote that “it is generally known that antitubercular drugs have no effect on the treatment of generalized BCG tuberculosis in immunodeficient children.” In 1977, Genin et al. [64] referred to the inevitable progression to death within 6 months in immunocompromised patients with generalized disease in spite of antimicrobial therapy.

There is little published information about regimens that are useful in the treatment of disseminated BCG disease that occurs after vaccination. However, there are therapeutic precedents established for other types of infection caused by BCG. Therapy for disseminated disease following intravesical instillation of BCG should include isoniazid, rifampin, and a corticosteroid. Therapy for disseminated BCG disease in immunocompromised hosts is limited, but this therapy is another obvious model for disseminated BCG disease. Ten patients with M. bovis infection in a Spanish review [69] all received therapy with isoniazid, rifampin, and ethambutol. Nine patients were cured and had no relapses, and one patient died of other causes.
In another retrospective review [70], most M. bovis isolates from 73 patients were sensitive to first-line antituberculous drugs (except pyrazinamide, to which M. bovis is uniformly resistant), and nearly all patients responded to therapy.

The antimycobacterial regimens used to treat patients whose cases were identified in our review are listed in tables 3 and 4. Isoniazid, rifampin, ethambutol, and streptomycin were most commonly used. It is striking that >70% of patients died even when their cases were aggressively managed. Plausible explanations for this high mortality rate include associated immunodeficiencies, delay in diagnosis or treatment (case 3), initial treatment with pyrazinamide to which BCG is uniformly resistant (cases 18 and 22), and the emergence of resistance to therapy (case 24) [63]. The high mortality rate may be a result of reporting bias.

Experience in the treatment of patients with AIDS and other mycobacterial diseases may provide principles for the treatment of immunocompromised patients with disseminated BCG disease. Poor drug absorption, drug interactions, and frequent adverse drug reactions have been observed to complicate therapy for mycobacterial infections in patients with AIDS [71–74]. Prolonged therapy is recommended for patients with AIDS and M. tuberculosis [75] or M. avium complex infections [76].

Implications for strategies for BCG vaccination. Vaccination strategies attempt to balance risk and benefit. The benefit of BCG immunization against M. tuberculosis infection has been the subject of much controversy and is beyond the scope of this article. A summary of trials on the efficacy of BCG vaccine has recently been published [77]. Virtually nothing is known about the efficacy of BCG vaccine for infants with HIV infection. However, HIV infection greatly increases the incidence of tuberculosis, so even a small degree of efficacy would have a major impact [78]. In addition to the effects on tuberculosis, BCG vaccine may also prevent other mycobacterial diseases, including cervical lymphadenitis due to atypical mycobacteria [79, 80] and Hansen’s disease [81].

The risks associated with BCG vaccination include local complications, extraregional localized disease, and disseminated BCG disease. The mortality attributable to disseminated BCG disease may be limited, since most patients have fatal underlying diseases. However, because of the emergence of HIV infection, the incidence of disseminated disease is probably greater than that (1.56 cases per 1 million BCG-vaccinated individuals) found by Lotte et al. [30].

Current recommendations regarding BCG vaccination vary, reflecting different risk/benefit settings. In settings where prenatal screening for HIV infection is not available and the risk of tuberculosis is high, the World Health Organization [82] recommends vaccinating all children not symptomatic for HIV infection. In developed countries, prenatal screening for HIV infection is becoming routine. The Advisory Committee on Immunization Practices in the United States [83] emphasizes withholding BCG vaccination from HIV-infected patients regardless of symptoms in regions in which the risk of tuberculosis is low.

The American Academy of Pediatrics [84] recommends that a child who receives BCG vaccination but does not have a positive reaction to the tuberculin test be revaccinated. The benefit of this second BCG vaccination for prevention of tuberculosis is not established, but our review indicates that there are risks associated with this practice. Patients with severe immunodeficiencies (including AIDS and severe combined immunodeficiency) are often anergic and would be selected for repeated vaccination by this policy. Three cases of disseminated BCG disease (nos. 24, 30, and 36) developed after revaccination because of a negative tuberculin test.

Case reporting. Confirmed or suspected cases of disseminated BCG disease should be reported in the medical literature and to the appropriate authorities. Because disseminated BCG disease is caused by an adverse drug reaction, cases should be reported to vaccine manufacturers (in the United States, Organon Teknika, Durham, NC [800-842-3220]) and the Vaccine Adverse Event Reporting System (800-822-7967). The corresponding author of this article (R.F.) would be pleased to collaborate in the definite identification of possible BCG isolates.

Acknowledgments

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Note Added in Proof

A new method of BCG identification was applied to cultures that were killed using ethanol and shipped without hazard at room temperature [85]. This method is available to clinicians worldwide for confirmation of BCG complications.

References


53. van Soolingen D, Hermans PWM, de Haas PEW, van Embden JDA. Insertion element IS1081-associated restriction fragment length poly-


