Spectrum of Bacille Calmette-Guérin (BCG) Infection after Intravesical BCG Immunotherapy

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Intravesical instillation of bacille Calmette-Guérin (BCG) effectively treats transitional cell carcinoma of the bladder. Occasionally, BCG infection complicates such treatment. In some patients, infection appears early (within 3 months after instillation) and is characterized by generalized symptoms, with pneumonitis and hepatitis. Late-presentation disease occurs >1 year after the first BCG treatment and usually involves focal infection of the genitourinary tract (the site at which bacteria were introduced) and/or other sites that are typical for reactivation of mycobacterial disease, such as the vertebral spine or the retroperitoneal tissues. Noncaseating granulomas are found in the majority of cases, whether early or late. Most patients respond to treatment with antituberculous drugs; in early-presentation disease, when features of hypersensitivity predominate, glucocorticosteroids are sometimes added. Late localized infection often requires surgical resection.

Since Morales et al. [1] first described intravesical infusion of bacillus Calmette-Guérin (BCG) to treat superficial bladder cancer, immunotherapy with BCG has become an effective alternative to chemotherapy in the management of this disease. This treatment has been shown to eradicate residual tumors in ≥60% of patients with papillary carcinoma and in ≥70% of patients with carcinoma in situ [2]. BCG, a live, attenuated strain of Mycobacterium bovis [3], interacts with the immune system to produce systemic immunity to BCG [4]. The antitumor activity, however, appears to be a local phenomenon [4], in which the mechanism of action of BCG in bladder cancer probably is specific anti-BCG cell-mediated immunity [4, 5]. In addition to T helper cells, cytotoxic T cells, natural killer cells, lymphokine-activated killer cells, and BCG-activated killer cells appear to be important in the process of eliminating malignant cells [4, 6, 7].

Intravesical treatment with BCG appears to be relatively safe. In a series of 2026 treated patients, <5% had major adverse reactions, which included granulomatous prostatitis, pneumonitis, hepatitis, sepsis, and hypersensitivity reactions [2, 8–10]. Clinically important infections have been reported relatively infrequently. We describe a series of patients in whom intravesical infusion of BCG was followed by disseminated or localized infection.

METHODS

Case retrieval. Four patients were treated by one of the authors, 3 at Henry Ford Hospital (Detroit; O.Y.G. or I.R.) and 1 at Memorial Hermann Southwest Hospital (Houston; E.J.S.). An additional 4 patients (3 at the University of Texas M. D. Anderson Cancer Center and 1 at Methodist Hospital) were identified through the Houston Tuberculosis Initiative at Baylor College of Medicine, an ongoing prospective study that identifies Mycobacterium isolates from clinical microbiology laboratories in Harris County, Texas.
A search of medical records at Henry Ford Hospital and M. D. Anderson Cancer Center yielded no other cases in which the discharge diagnosis was disseminated BCG infection. The medical records of all 8 patients were reviewed by the principal investigator (O.Y.G.).

All patients underwent intravesical instillation of BCG for the treatment of biopsy-proven bladder cancer. In our cases, the source of the BCG was identified as the Tice strain (TICE BCG [Organon]; each vial contains $1 \times 10^8$–$8 \times 10^8$ cfu).

**Microbiological isolation.** Standard techniques for cultures (Middlebrook and Löwenstein-Jensen media) and staining (acid-fast bacillus auramine stain) were used in each hospital laboratory. Speciation of the *Mycobacterium tuberculosis* complex was done for 2 isolates by biochemical methods at the M. D. Anderson Cancer Center Laboratory. Differentiation between *M. tuberculosis*, *M. bovis*, and BCG was made for 2 additional isolates at the Baylor College of Medicine Tuberculosis Research Laboratory by means of standardized restriction fragment–length polymorphism analysis of the IS6110 repetitive element and by spoligotyping.

**Literature search.** A computer-assisted search of the English literature (using MEDLINE, covering years 1966–2002) identified case reports of disseminated BCG infection or hypersensitivity associated with bladder instillation therapy from the United States and Canada. Keywords used in the search were “BCG infection,” “BCG complication,” and “bladder cancer,” singly and in combination. In addition to the MEDLINE search, publications referenced in the footnotes of other case reports were obtained and reviewed.

**RESULTS**

**Summary of Data from Our 8 Cases**

**Sociodemographic characteristics.** The mean age of our 8 patients (±SD) was 63.8 ± 11.9 years (range, 44–77 years); all were male. They were generally in good health, although they had medical conditions associated with their age, including hypertension (6 patients), coronary artery disease (3 patients), and diabetes mellitus (3 patients). One patient was undergoing hemodialysis for end-stage renal disease due to diabetes and hypertension. None had known exposure to carcinogens and none was taking immunosuppressive medications.

**BCG treatments.** Patients received 6–10 intravesical instillations of the Tice strain of BCG (mean ± SD, 6.8 ± 1.4 treatments), generally at weekly intervals, to treat bladder cancer (table 1). Data on doses were not available, but the general practice is to reconstitute 1 vial of TICE BCG per instillation. During the course of therapy, symptoms of cystitis were common, characterized by dysuria, urgency, and hematuria. One patient experienced a flulike illness shortly after each instillation.

**Clinical characteristics of BCG infection.** The clinical course of BCG-related disease in our 8 patients (table 1) suggested that BCG infections could be stratified into early and late presentation, as illustrated by the cases of patients 1 and 6.

Patient 1 (early presentation), a 68-year-old man, had received a diagnosis of transitional cell carcinoma of the bladder. The tumor was excised, and a series of 7 weekly instillations of BCG was given. Eight to 10 weeks after the first instillation,
the patient noted the gradual onset of fever, chills, malaise, fatigue, night sweats, weight loss, and shortness of breath. One month later, his temperature was 39°C, respiratory rate was 22 breaths/min, and O₂ saturation was 89%. The patient had diffuse crackles in both lung fields and mild tenderness in the right upper quadrant of the abdomen. The hemoglobin level and WBC count were normal; the platelet count was 127,000 platelets/mm³. The following liver enzyme levels were noted: aspartate aminotransferase, 150 IU/L; alanine aminotransferase, 369 IU/L; alkaline phosphatase, 252 IU/L; and total bilirubin, 1.3 mg/dL. Tests for viral hepatitis yielded negative results. Image studies included chest radiography, which revealed a miliary pattern, and an abdominal ultrasound, which found no abnormalities. Results of culture of blood, urine, and sputum samples were negative for common bacteria, mycobacteria, and fungi. Examination of specimens from a transbronchial biopsy of the lung showed multiple noncaseating granulomas; acid-fast bacilli were not seen, and cultures of BAL fluid and biopsy tissue yielded negative results. Isoniazid, rifampin, and ethambutol were prescribed, and the symptoms resolved after the first week of treatment. The patient stopped antibiotic treatment after a total of 6 weeks because of severe gastrointestinal intolerance. Eight months later, he was still free of symptoms; pulmonary infiltrates and liver enzyme abnormalities had resolved.

Within a few weeks of completing a course of therapy with intravesical BCG, patient 1 developed BCG infection, which progressed in a manner similar to that of disseminated tuberculosis until antituberculous therapy was given. Although many noncaseating granulomas were seen on histologic examination, culture results were negative for M. bovis, a finding that has led some observers to emphasize the role of hypersensitivity as the cause of symptoms [12–18]; this concept derives support from the rapidity and completeness of the response to only 6 weeks of therapy. The response to treatment is also consistent with the idea that host immunity may become effective once treatment is given for infection caused by a pathogen with relatively low-grade virulence.

Patient 6 (late presentation), a 53-year-old diabetic man, had undergone surgical intervention for transitional cell carcinoma of the bladder, followed by BCG therapy. One year later, the patient presented with hematuria and symptoms of urinary obstruction. Physical examination revealed a prostatic mass. Results of blood count and liver enzyme measurements were normal, and no abnormalities were seen on chest radiography. Examination of specimens from biopsy of the prostate revealed noncaseating granulomas; culture yielded M. bovis. The patient received isoniazid and rifampin for 6 months, and the infection resolved.

After BCG was instilled into the bladder of this diabetic man, viable organisms persisted, but further dissemination did not occur, presumably because of an efficient immune response. One year later, in a manner analogous to reactivation tuberculosis, infection became clinically apparent at the site of initial inoculation.

**Early-presentation disease.** In 5 patients (patients 1–5; table 1), symptoms suggesting a subacute generalized infection appeared within 8–12 weeks after the first BCG treatment. These patients all had fever and malaise; chills, sweats, weight loss, shortness of breath, and arthralgia were also present, in varying proportions (table 2). Three of these patients (patients 1–3) had a clinical picture of disseminated disease with pneumonitis (diffuse interstitial infiltrates) and hepatitis; 1 patient also had polyarthritis. The patients had WBC counts of 3500–4500 cells/mm³ and platelet counts <150,000 platelets/mm³. One patient (patient 4), who was undergoing hemodialysis for end-stage renal disease, had hematogenous spread of organisms to the peritoneum. In patient 5, BCG infection of the prostate, which manifested as fever, chills, night sweats, and weight loss, in addition to urinary symptoms, appeared within 12 weeks of the first treatment.

The diagnosis of disseminated BCG infection in 4 of these 5 cases was supported by the finding of noncaseating granulomas in biopsied tissues (lung, liver, prostate, and peritoneum, in 1 patient each) (table 3). Patient 3 was diagnosed on the basis of clinical findings and therapeutic response. Cultures for mycobacteria were done for all patients but yielded positive results in only 1 case. No further molecular techniques for identifying structural elements of M. bovis (e.g., DNA probe), were done for culture-negative patients. Four patients had rapid responses to treatment with antituberculous drugs; glucocor-

### Table 2. Symptoms in patients with early or late presentation of bacille Calmette-Guérin (BCG) infection after treatment with instilled BCG.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Early presentation (n = 5)</th>
<th>Late presentation (n = 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Chills</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Sweats</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Weight loss</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Malaise</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Arthralgia/Arthritis</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Ascites</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Urinary symptoms</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Testicular or prostatic mass</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>
ticostereoids were added to the regimen for 1 patient. In patient
1, treatment was discontinued after only 6 weeks, but disease
did not recur. In general, the outcome of treatment of culture-
negative patients with antituberculous drugs was favorable
(table 1).

Late-presentation disease. Three patients (patients 6–8;
table 1) had no symptoms of BCG infection until >1 year after
the first instillation (mean interval between instillation of BCG
and onset of symptoms, 15.7 months). These patients then
developed disease localized to the genitourinary tract (a testicular
mass in 2 patients and a prostatic mass in 1 patient) in the
absence of laboratory or radiographic findings of hepatitis or
pneumonitis. None of these patients had generalized symptoms
such as fever and chills.

Examination of biopsy specimens of the affected tissues re-
vealed noncaseating granulomas. Special stains for mycobac-
teria such as fever and chills. None of these patients had generalized symptoms
absence of laboratory or radiographic findings of hepatitis or
mass in 2 patients and a prostatic mass in 1 patient) in the
veloped disease localized to the genitourinary tract (a testicular
and onset of symptoms, 15.7 months). These patients then de-
veloped disease localized to the genitourinary tract (a testicular

Table 3. Results of histological studies and mycobacterial cul-
tures for 8 patients who developed bacille Calmette-Guérin (BCG)
infection or hypersensitivity reaction after treatment with in-
stilled BCG.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Source of specimen</th>
<th>Pathologic finding</th>
<th>Microbiologic finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Lung</td>
<td>Noncaseating granuloma</td>
<td>No growth</td>
</tr>
<tr>
<td>2</td>
<td>Liver</td>
<td>Noncaseating granuloma</td>
<td>No growth</td>
</tr>
<tr>
<td>3</td>
<td>—</td>
<td>Not done</td>
<td>Not done</td>
</tr>
<tr>
<td>4</td>
<td>Peritoneum</td>
<td>Noncaseating granuloma</td>
<td>BCGa</td>
</tr>
<tr>
<td>5</td>
<td>Prostate</td>
<td>Noncaseating granuloma</td>
<td>No growth</td>
</tr>
<tr>
<td>6</td>
<td>Prostate</td>
<td>Noncaseating granuloma</td>
<td>BCGa</td>
</tr>
<tr>
<td>7b</td>
<td>Testicle</td>
<td>Noncaseating granuloma</td>
<td>M. bovis</td>
</tr>
<tr>
<td>8b</td>
<td>Testicle</td>
<td>Noncaseating granuloma</td>
<td>M. bovis</td>
</tr>
</tbody>
</table>

a Differentiated from Mycobacterium bovis by spoligotyping.
b Patients 7 and 8 have been described elsewhere [11].

Characterization of Previously Reported Cases

A review of all reports of BCG infection from the United States
and Canada from January 1966 through May 2002 [3, 11, 13,
16, 19–40] identified 35 patients (including our patients 7 and
8 [patients 21 and 22 in the review], who have been described
elsewhere [11]) for whom sufficient clinical information was
available to enable stratification into early or late syndromes,
on the basis of whether the patient presented for medical at-
tention within 6 months (usually within 3 months) or >6
months (usually ≥1 year) after bladder instillation of BCG.
These cases are summarized in tables 4 and 5.

The mean age of these patients (±SD) was 66.5 ± 8.9 years
(range, 47–90 years), and the mean number of BCG instillations
(±SD) was 7.8 ± 4.8, similar that for our 8 patients. The time
at which symptoms appeared in relation to the first treatment
was variable. When patients were stratified into those with early
and those with late presentation, distinct syndromes emerged,
closely paralleling those of our 8 patients. Twenty had early-
presentation disease (mean time after the first BCG instillation
[±SD], 9.4 ± 5.8 weeks), characterized by generalized symp-
toms and disseminated involvement (usually systemic mani-
festations involving sites distant from the bladder), whereas 15
had late-presentation disease (mean time after the first BCG
instillation [±SD], 75.9 ± 48.3 weeks); in most cases, the in-
fec tion was localized, with no systemic manifestations.

Eighteen (90%) of 20 patients with early disease had pneu-
monitis and/or hepatitis at presentation, compared with 4
(27%) of 15 in the late-disease group (OR, 24.75; 95% CI,
3.12–277.46; P < .001). Five of these patients were sufficiently
ill that they were judged to be septic. An area of localized
infection was present in 9 (60%) of 15 patients with late pre-
sentation but in none of the patients with early presentation
(P < .001).

Noncaseating granulomas were found in a similar proportion
among patients with early presentation and patients with late
presentation (12 [71%] of 17 vs. 9 [69%] of 13; P = 1.0), but
culture of biopsied tissue was less likely to yield M. bovis for
patients with early than for patients with late disease (5 [31%]
of 16 vs. 9 [64%] of 14; OR, 0.25; P = .08).

As might be expected, there was no consistent approach to
treatment. However, outcomes were similar, regardless of reg-
imen used. Patients were treated by different physicians at sev-
eral medical centers. All but 1 patient with early-presentation
disease received antituberculous therapy; 4 also received glu-
corticosteroids, which were thought by the treating physician
to contribute to the rapidity of response. Of 11 patients with
late disease and localized infection, 9 underwent surgical re-
section, and 3 of these received no further antituberculous
therapy.

**DISCUSSION**

Since the initial report in 1976 that intravesical instillation
of BCG reduced the rate of recurrence of superficial transitional
 cell carcinoma [1, 33], the superiority to chemotherapy and
the safety of BCG immunotherapy have been repeatedly con-
firmed [2, 10, 41]. The Southwest Oncology Group reported
a response rate of 87%, with an estimated 4-year disease-free
rate of 83% [2, 42, 43]. The mechanism of action is thought
to be BCG-mediated modulation of the immune response in
Table 4. Summary of findings for 20 patients who developed early-presentation disseminated bacille Calmette-Guerin (BCG) infection or hypersensitivity.

<table>
<thead>
<tr>
<th>Patient [ref.]</th>
<th>Patient age, years</th>
<th>Syndrome</th>
<th>No. of BCG instillations</th>
<th>Time to symptoms*</th>
<th>Liver enzyme levels at onset of symptoms</th>
<th>Pathologic finding</th>
<th>M. bovis detected on culture</th>
<th>Tissue specimen</th>
<th>Findings of chest radiography</th>
<th>Treatment for BCG-related symptoms</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 [26]</td>
<td>62</td>
<td>Hepatitis</td>
<td>7</td>
<td>5 weeks</td>
<td>AST/ALT, IU/L, 97/79, AP, IU/L, 148</td>
<td>NCG</td>
<td>No</td>
<td>NA</td>
<td>Liver</td>
<td>INH, Rif</td>
<td>Resolution</td>
</tr>
<tr>
<td>2 [16]</td>
<td>49</td>
<td>Pneumonitis, hepatitis, pancytopenia</td>
<td>1</td>
<td>&lt;1 h</td>
<td>125/84, 138, WNL, 5.7</td>
<td>PDG</td>
<td>No</td>
<td>NA</td>
<td>Lung, BM</td>
<td>INH, Rif, steroids, plasmapheresis</td>
<td>Resolution</td>
</tr>
<tr>
<td>3 [31]</td>
<td>78</td>
<td>Pneumonitis, hepatitis</td>
<td>10</td>
<td>22 weeks</td>
<td>NA, NA, Lung</td>
<td>NCG</td>
<td>No</td>
<td>NA</td>
<td>Miliary pattern</td>
<td>INH, Rif, Eth</td>
<td>Resolution</td>
</tr>
<tr>
<td>4 [21]</td>
<td>54</td>
<td>Hepatitis</td>
<td>4</td>
<td>16 weeks</td>
<td>66/120, 702, NA, NA, BM</td>
<td>NG</td>
<td>Yes*</td>
<td>NA</td>
<td>RLL</td>
<td>INH, Rif, Cyse</td>
<td>Resolution</td>
</tr>
<tr>
<td>5 [32]</td>
<td>61</td>
<td>Hepatitis</td>
<td>6</td>
<td>10 weeks</td>
<td>NA, 157, WNL</td>
<td>NCG, MTCi</td>
<td>No</td>
<td>No</td>
<td>WNL</td>
<td>INH, Rif, steroids</td>
<td>Resolution</td>
</tr>
<tr>
<td>6 [25]</td>
<td>69</td>
<td>Pneumonitis, hepatitis</td>
<td>6</td>
<td>&lt;1 h</td>
<td>NA, 113, 333, Lung</td>
<td>NCG</td>
<td>Yes</td>
<td>NA</td>
<td>Miliary pattern</td>
<td>Rif, PZA, Sm, Rif, Em</td>
<td>Resolution</td>
</tr>
<tr>
<td>7 [13]</td>
<td>69</td>
<td>Pneumonitis</td>
<td>6</td>
<td>12 weeks</td>
<td>NA, NA, Lung</td>
<td>CG</td>
<td>No</td>
<td>NA</td>
<td>Miliary pattern</td>
<td>INH, Rif, PZA</td>
<td>Resolution</td>
</tr>
<tr>
<td>8 [23]</td>
<td>72</td>
<td>Hepatitis, DIC</td>
<td>1</td>
<td>Hours</td>
<td>694/534, 136, 2.4</td>
<td>NCG</td>
<td>Yes*</td>
<td>NA</td>
<td>WNL</td>
<td>INH, Rif, Em</td>
<td>Resolution</td>
</tr>
<tr>
<td>9 [24]</td>
<td>57</td>
<td>Pneumonitis</td>
<td>9–10</td>
<td>13 weeks</td>
<td>NA, NA, Lung</td>
<td>NCG</td>
<td>Yes</td>
<td>NA</td>
<td>Miliary pattern</td>
<td>INH, Rif, PZA, Em, steroids</td>
<td>Resolution</td>
</tr>
<tr>
<td>10 [29]</td>
<td>67</td>
<td>Pneumonitis, hepatitis, pancytopenia</td>
<td>4</td>
<td>8 weeks</td>
<td>1, 1, 1, NA, BM</td>
<td>NCG</td>
<td>No</td>
<td>NA</td>
<td>Intestinal infiltrates</td>
<td>Rif, Em</td>
<td>Resolution</td>
</tr>
<tr>
<td>11 [29]</td>
<td>75</td>
<td>Pneumonitis, erythema multiforme</td>
<td>3</td>
<td>12 weeks</td>
<td>NA, NA, Lung</td>
<td>NCG</td>
<td>No</td>
<td>NA</td>
<td>Intestinal infiltrates</td>
<td>Rif, Em</td>
<td>Resolution</td>
</tr>
<tr>
<td>12 [28]</td>
<td>68</td>
<td>Pneumonitis</td>
<td>6</td>
<td>4 weeks</td>
<td>NA, NA, NA, Lung</td>
<td>CG</td>
<td>No</td>
<td>NA</td>
<td>Intestinal infiltrates</td>
<td>Steroids</td>
<td>Resolution</td>
</tr>
<tr>
<td>13 [37]</td>
<td>74</td>
<td>Hepatitis</td>
<td>5</td>
<td>4 weeks</td>
<td>350/630, 142, NA</td>
<td>NCG</td>
<td>No</td>
<td>NA</td>
<td>Liver</td>
<td>INH, Rif</td>
<td>Resolution</td>
</tr>
<tr>
<td>14 [35]</td>
<td>67</td>
<td>Pneumonitis, hepatitis</td>
<td>16</td>
<td>14–16 weeks</td>
<td>55/50, 339, NA</td>
<td>NCG</td>
<td>No</td>
<td>NA</td>
<td>Miliary pattern</td>
<td>Rif, Em, LEV</td>
<td>Resolution</td>
</tr>
<tr>
<td>15 [22]</td>
<td>70</td>
<td>Sepsis</td>
<td>4</td>
<td>4 weeks</td>
<td>NA, NA, NA, NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>INH</td>
<td>Death</td>
</tr>
<tr>
<td>16 [22]</td>
<td>66</td>
<td>Sepsis, DIC, hepatitis</td>
<td>7</td>
<td>5 weeks</td>
<td>1, NA, NA, Lung, liver, kidney</td>
<td>NG</td>
<td>Yes</td>
<td>NA</td>
<td>NA</td>
<td>INH, Rif</td>
<td>Death</td>
</tr>
<tr>
<td>17 [22]</td>
<td>63</td>
<td>Sepsis, multiorgan failure, hepatitis</td>
<td>6</td>
<td>6 weeks</td>
<td>NA, NA, NA, Liver, bone, spleen, kidneys</td>
<td>NCG</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>INH, Rif, Stm</td>
<td>Death</td>
</tr>
<tr>
<td>18 [22]</td>
<td>65</td>
<td>Sepsis, DIC, hepatitis</td>
<td>11</td>
<td>11 weeks</td>
<td>NA, 1, NA, NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>INH, Rif, Cyse</td>
<td>Resolution</td>
</tr>
<tr>
<td>19 [22]</td>
<td>63</td>
<td>Sepsis, pneumonia, hepatitis</td>
<td>3</td>
<td>3 weeks</td>
<td>NA, NA, NA, NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>INH, Rif, Cyse, Rif, Em, PZA</td>
<td>Resolution</td>
</tr>
<tr>
<td>20 [36]</td>
<td>67</td>
<td>Aortoiliac aneurysms, testicular mass, ARF</td>
<td>3</td>
<td>12–16 weeks</td>
<td>WNL, WNL, WNL</td>
<td>NCG, AFB</td>
<td>No</td>
<td>NA</td>
<td>None</td>
<td>None</td>
<td>Death</td>
</tr>
</tbody>
</table>

NOTE. AFB, acid-fast bacilli; ALT, alanine aminotransferase; Amik, amikacin; AP, alkaline phosphatase; ARF, acute renal failure; AST, aspartate aminotransferase; Bil, total bilirubin; BM, bone marrow; CG, caseating granuloma; Cyse, cycloserine; DIC, disseminated intravascular coagulation; Em, erythromycin; Eth, ethambutol; INH, isoniazid; LEV, levofloxacin; M. bovis, Mycobacterium bovis; MTC, Mycobacterium tuberculosis complex; NA, not available; NCG, noncaseating granuloma; NG, no granuloma; PDG, poorly defined granuloma; Ofx, ofloxacin; PZA, pyrazinamide; ref., reference; Rif, rifampin; Sm, streptomycin; WNL, within normal limits; f, increased.

* Interval between first instillation and onset of symptoms.

b Urine specimen.

c Positive results of DNA probe.

d Death was due to myocardial infarction.

e Blood sample.

f And <1 h after the final BCG instillation.

g Tissue specimens from multiple organs.
Table 5. Summary of findings for 15 patients who developed late-presentation disseminated bacille Calmette-Guérin (BCG) infection or hypersensitivity.

| Patient [ref.] | Patient age, years | Syndrome | No. of BCG instillations | Time to symptoms, weeks<sup>a</sup> | AST/ALT, IU/L | AP, IU/L | Bil, mg/dL | Tissue specimen | Pathologic findings | M. bovis detected on culture | Findings of chest radiography | Treatment for BCG-related symptoms | Outcome |
|---------------|--------------------|----------|--------------------------|-------------------------------------|---------------|----------|-----------|----------------|---------------------|----------------------|---------------------------|-----------------------------|-----------------------------|----------|
| 21 [11]       | 54                 | Testicular mass | 6                        | 64–72                               | NA/15         | 79       | 0.5       | Testis          | NCG                 | Yes                  | WNL                      | Surgery                     | Resolution                |
| 22 [11]       | 69                 | Testicular mass | 7                        | 64–72                               | NA/25         | NA       | 0.7       | Testis          | NCG                 | Yes                  | WNL                      | Surgery, INH               | Resolution                |
| 23 [27]       | 79                 | Testicular masses, enlarged prostate | 6                        | 24                                 | NA/NA        | NA/NA    | NA        | Testis, prostate | NCG, AFB             | No                   | NA                       | INH, surgery               | Resolution                |
| 25 [19]       | 72                 | Mycotic vascular infection | 6                        | NA                                 | NA/NA        | NA/NA    | NA        | Femoral graft   | NA                  | Yes<sup>b</sup> | NA                       | INH, Rif, Em, surgery     | Resolution                |
| 26 [19]       | 58                 | Mycotic vascular infection | 12                       | 156                                | NA/NA        | NA/NA    | NA        | Aorta           | NCG                 | Yes                  | NA                       | INH, Rif, surgery          | Resolution                |
| 27 [19]       | 71                 | Mycotic vascular infection | NA                       | 52                                 | NA/NA        | NA/NA    | NA        | NA              | NCG                 | Yes                  | WNL                      | INH, Rif, Em, surgery      | Resolution                |
| 28 [39]       | 79                 | Vertebral osteomyelitis, paraspinal, psoas abscesses | 20                       | 48                                 | NA/NA        | NA/NA    | NA        | Vertebra        | NG                  | Yes                  | NA                       | INH, Rif, resolution        | Resolution                |
| 29 [3]        | 69                 | Psoas abscess, infected aortic aneurysm | 6                        | 156                                | NA/NA        | NA/NA    | NA        | Autopsy<sup>c</sup> | CG, AFB              | Yes                  | WNL                      | Surgery                     | Death            |
| 30 [34]       | 90                 | Tuberculous spondylitis | 6                        | 64                                 | NA           | ↑ NA     | NA        | Bone            | NCG                 | Yes                  | NA                       | INH, Rif, Em               | Resolution                |
| 31 [38]       | 47                 | Chest wall mass | >20                      | 166                                | WNL          | WNL      | WNL       | Mass and rib    | NCG, AFB             | No                   | WNL                      | INH, Rif, surgery          | Resolution                |
| 32 [30]       | 73                 | Pneumonitis, hepatitis | 9                        | 36                                 | 95/122       | 125      | 1.2       | Lung            | NCG                 | No                   | Miliary pattern           | INH, Rif, Em, PZA         | Resolution                |
| 33 [38]       | 64                 | Hepatitis, ARF, rhabdomyolysis | >9                       | 24<sup>d</sup>                     | 10× NV/NA    | NA/NA    | NA        | Kidney          | ATN                 | No                   | WNL                      | None                       | Resolution                |
| 34 [40]       | 57                 | Hepatitis | 13                       | 52                                 | 203/311      | 635      | 12.2      | Liver           | NCG                 | Yes<sup>e</sup> | WNL                      | Ofx, Em, Amik              | Resolution                |
| 35 [33]       | 63                 | Sepsis, pneumonitis, DIC, testicular mass | 10–14                   | 52–80<sup>f</sup> | 192/NA     | NA/NA    | NA        | Autopsy<sup>c</sup> | CG                  | No                   | WNL                      | INH, Rif, steroids         | Death<sup>g</sup> |

NOTE. AFB, acid-fast bacilli; ALT, alanine aminotransferase; Amik, amikacin; AP, alkaline phosphatase; ARF, acute renal failure; AST, aspartate aminotransferase; Bil, total bilirubin; CG, caseating granuloma; Cyse, cycloserine; DIC, disseminated intravascular coagulation; Em, erythromycin; Eth, ethambutol; INH, isoniazid; LEV, levofloxacin; M. bovis, Mycobacterium bovis; NA, not available; NCG, noncaseating granuloma; NG, no granuloma; NV, normal value; PDA, poorly defined granuloma; Ofx, ofloxacin; PZA, pyrazinamide; ref., reference; Rif, rifampin; Stm, streptomycin; WNL, within normal limits; ↑, increased.<br>I. Interval between first instillation and onset of symptoms.<br>b. Sputum sample was also tested.<br>c. Tissue specimens from multiple organs.<br>d. And <1 h after the final BCG instillation.<br>e. Blood sample.<br>f. Death was due to pulmonary embolism.
the bladder, resulting in inflammation and subsequent elimination of the tumor [7]. Immunohistochemical studies and animal models show that an intact immune system, particularly the cellular system (CD4/CD8), is required for antitumor activity [4, 7, 44].

The local immune response is complex, but presentation of mycobacterial antigen by phagocytes to T helper cells is the pivotal interaction. This presentation requires a series of cell-surface interactions, including that of processed antigen with T cell receptor, major histocompatibility complex class II antigen with CD4, lymphocyte function antigen 1 with intracellular adhesion molecule 1, and CD28 with CD80 [4]. During and after intravesical BCG therapy for transitional cell carcinoma, tumor cells take on features of BCG-infected phagocytes, which then exert antitumor activity. Experimental studies show that tumor cells are active in the immune response that occurs in the bladder wall, which suggests that the interaction between BCG and tumor cells may be as important in the immune response as that between BCG and professional phagocytes [4, 45, 46]. Interestingly, prior publications have also demonstrated the important role of natural killer cells, lymphokine-activated killer cells, and BCG-activated killer cells in the elimination of tumor cells [4].

Inoculating a viable infectious agent into the bladder raises the potential risk of local or generalized infection, just as has been described following intradermal BCG vaccination for prevention of tuberculosis [47, 48]. Not surprisingly, soon after the initial description of BCG treatment for bladder cancer, the first such report appeared. In early publications, urologic trauma was said to contribute to dissemination of BCG [10, 17, 22, 25, 36, 49]; in fact, these cases differed very little, if at all, from later cases or from the ones we now report, in which traumatic instillation was not documented.

Our analysis revealed that BCG infections that occurred after intravesical therapy could be stratified into early- and late-presentation disease. Of the total of 41 patients analyzed in this report (8 of ours and 35 previously described [11], of which 2 are duplicated), 25 had early-presentation disease. Usually, within 3 months of the original BCG treatment, these individuals had an illness characterized by fever, generalized symptoms, and evidence of systemic infection, with involvement of the liver and lungs in nearly every case. Biopsies were done in 17 cases, and examination of biopsy specimens uniformly revealed granuloma; cultures for mycobacteria, however, yielded positive results in only 5 of the 17 cases.

This early-presentation disease results from systemic infection by a relatively low-grade pathogen in an immunologically competent host. Within a few weeks of the first dose, the host becomes sensitized to BCG. As organisms proliferate, and as repeated instillations of BCG introduce additional organisms, a generalized granulomatous response develops. Immunologic competence of the host, together with low virulence of the organism, results in granulomas that are well formed and in which organisms cannot be detected; including previously reported cases and the cases we have added, culture results in this group were positive in 6 (30%) of 20 cases. Interestingly, the 1 patient with early-presentation disease who was known to have a preexisting immunosuppressive condition (the patient was undergoing hemodialysis because of diabetic renal failure) had peritonitis with granulomas from which BCG was cultured. Every patient with early disease did not necessarily fit this hypothesis; for example, 1 had focal disease of the genitourinary tract and an infected aneurysm.

In contrast, among the 16 patients with late presentation, 12 had localized disease involving the genitourinary tract (5 patients), the vascular tree (4 patients), vertebral bones (2 patients), retroperitoneal soft tissues (2 patients), and the chest wall (1 patient). The total number exceeds the actual number of patients because multiple areas were involved in some cases. This late syndrome results from reactivation of infection after successful immunologic control of early dissemination. Izes et al. [3] reported a case in which administration of glucocorticoids 3 years after BCG therapy was followed by reactivation of BCG infection. Disease appears at the site that was exposed to the highest inoculum (the genitourinary tract), by either contiguous or hematogenous spread, or in other sites that are characteristically involved by extrapolmonary dissemination of tuberculosis. Granulomas are uniformly present. Culture of the involved tissue yielded positive results in 10 (67%) of 15 cases of late-presentation disease. Only 4 patients with late-presentation disease had symptoms and signs of generalized infection, and 2 of these presented with sepsis. The involvement of BCG infection in infected aneurysms, as reported in 4 cases of late-presentation and 1 of early-presentation disease, remains unexplained. Such infections are exceedingly rare in tuberculosis. Efforts to differentiate M. bovis from M. tuberculosis should be pursued, because our patient population belongs to a generation in which tuberculosis was more prevalent, and the clinical presentation could represent a reactivation of a latent infection.

The inability to identify M. bovis in affected tissues in every case is not entirely unexpected. Whereas granulomas are typically seen, acid-fast stains and cultures, especially in early-presentation cases, yield negative results, as do DNA hybridization studies [8, 10]. Some authorities use the negative culture results to support their hypothesis that the granulomas in BCG disease result from a hypersensitivity reaction, not an infection [12, 14–16]; however, the presence of antigens, such as live organisms or at least structural elements of dead M. bovis, is required to initiate a hypersensitivity reaction. The likelihood that BCG can be isolated through culture is affected by many factors, including the number of organisms present (which, in turn, reflects the ability of the immune system to control in-
fection), the handling of biopsied tissue, and culture technique [25]. In addition, highly sensitive and specific molecular techniques are needed to enhance the chance that these mycobacteria will be isolated. We attribute both early- and late-presentation diseases to active infection and the accompanying immune response, recognizing that, for a variety of reasons, tissue cultures may yield negative results in a varying proportion of cases. Organisms remain susceptible to isoniazid, rifampin, and ethambutol but highly resistant to pyrazinamide.

There has been no reported trial to assess optimal therapy for BCG infection. The role of steroids has also not been addressed in a prospective study. In the absence of data, and because the disease results from the interaction between mycobacterial infection and the immune state of the affected host, treatment is, by necessity, based on the choice of the individual physician. Nevertheless, it seems reasonable to treat patients for at least 9 months, because pyrazinamide (for which the treatment period is much shorter) should not be included in the regimen.

References