Pathologic Findings for Bacille Calmette-Guérin Infections in Immunocompetent and Immunocompromised Patients

Lulu Ahmad Al-Bhlal, MD, FRCPA, FKSUP

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Abstract

The pathologic findings from biopsy specimens from 9 patients with postvaccination bacille Calmette-Guérin (BCG) infection are presented. The patients were vaccinated with BCG during the first 2 days of life. Four patients had normal immunity and 5 patients were immunocompromised. The pathologic findings in both groups were different. Biopsy specimens from patients with normal immunity showed multiple epithelioid granulomas and Langhans giant cells with or without suppuration. Caseous necrosis was minimal. Ziehl-Neelsen stain for acid-fast bacilli showed a few bacilli in 2 cases and was negative in the remaining 2 cases. Biopsy specimens from the second group of patients, who were immunosuppressed, consisted mainly of skin and subcutaneous tissue. These revealed diffuse infiltrates of histiocytes with plump nuclei and abundant “dirty” grayish cytoplasm, which was full of numerous acid-fast bacilli. The clinical course for the 2 groups also was different. Patients with normal immunity generally recover completely, spontaneously or after excision of the suppurative lymph node and usually do not require antibiotic chemotherapy. In immunosuppressed patients, disseminated BCG infection, which may prove fatal, may develop. These patients should receive a full course of antituberculous chemotherapy and, in addition, treatment of the underlying immunologic disorder.

Vaccination of all newborn babies with bacille Calmette-Guérin (BCG) vaccine is a standard practice in Saudi Arabia. Although this practice generally is considered safe and effective, rare complications have occurred in approximately 1.9% of the infants.1 These complications include regional lymphadenopathy, subcutaneous abscess at the vaccination site, osteomyelitis, arthritis, and hepatic granulomas.2 Most of these complications are self-limiting and cause no serious morbidity. The associated disease is called “BCGitis.”

Children with defective immunity, on the other hand, may have more severe and disseminated mycobacterial infection. The reported incidence of more severe infection ranges between 0.72 and 3.4 per 1 million children in different series.3,4 Enlargement of regional lymph nodes with or without suppuration is a well-known sequela of BCG vaccination.1 It is important to recognize that invasion of regional lymph nodes by the avirulent strain of BCG is part of successful vaccination. The lymphadenitis is, however, subclinical and regresses spontaneously. Only when the regional lymph nodes are involved by abscess formation with suppuration do they become a source of concern to patients and physicians.1 The lymphadenitis usually is unaccompanied by systemic reaction.5

The frequency of lymphadenopathy ranges between 0.73% and 2.2% in different series.6,7 Lymphadenopathy can occur in persons with normal immune response and more often is seen in the younger age group, especially newborns.1 Most lymphadenopathy occurs during the first year of life, with a mean interval of 2.5 months.1,2,5 However, cases have been reported of postvaccination complications developing at 18 months of age4 and 3 years after receiving BCG vaccine.2
In patients with immunologic abnormalities, such as severe combined immunodeficiency, restricted cellular immunodeficiency, Swiss type hypogammaglobulinemia, thymic alymphoplasia, chronic granulomatous disease of childhood, and HIV infection, a disseminated BCG infection may develop after vaccination.\(^2,8,9\) The risk of developing this complication in healthy infants is very low. However, rare cases of fatal disseminated BCG infection in apparently healthy children have been reported.\(^10,11\) The literature on the pathologic changes in postvaccination BCG infections is scant.\(^8\) This article describes the pathologic findings for 9 patients with postvaccination BCG infections.

**Materials and Methods**

All patients with a histopathologic diagnosis of infection after receipt of BCG vaccine were identified from the files of the department of Pathology at King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia. A total of 9 cases thus identified during an 8-year period (1990-1997) form the basis for the present study. All patients were born in Saudi Arabia, and all had received BCG vaccine during the first 2 days of life.

The patient’s medical records, histologic slides of all biopsy specimens, and the pathology reports were reviewed. The slides included H&E-stained sections and sections stained with Ziehl-Neelsen stain for acid-fast bacilli and Gomori methenamine silver stain for fungi. The patients were classified into 2 groups. The first group included patients with normal immunity, and the second group included patients with known immunodeficiency. The microscopic features of both groups were studied. For 8 cases (all except case 2), specimens from lesions were submitted for culture. These specimens were cultured on Löwenstein-Jensen media for a period of 6 weeks. The incubation temperature was kept between 35 C and 37 C. Identification of positive growth of acid-fast bacilli was confirmed by negative niacin and negative nitrate reduction test results, catalase production at room temperature but not at 68 C, resistance to pyrazinamide and cycloserine, and sensitivity to thiophen-2-carboxylic hydrazide.\(^4\)

**Results**

The 4 patients with normal immunity ranged in age from 4 to 9 months at initial examination; 2 were boys and 2 were girls. In 3 cases (cases 1, 3, and 4), the left axillary lymph nodes were enlarged. In cases 1 and 4, a discharging sinus in the left axilla was noted, and in case 4, a skin nodule was found on the left lateral chest wall near the axilla. Hepatomegaly and elevated liver enzyme levels were present in case 2.

All patients with enlarged lymph nodes underwent lymph node biopsy. Microscopic examination showed multiple epithelioid granulomas, with Langhans giant cells. In case 3, some epithelioid granulomas showed central necrosis. In case 4, many stellate abscesses were present. A tru-cut needle biopsy of liver in case 2 showed multiple epithelioid granulomas in the portal tracts. No giant cells or caseous necrosis were present. Ziehl-Neelsen stain for acid-fast bacilli showed a few acid-fast bacilli in cases 1 and 4, while no acid-fast bacilli were found in cases 2 and 3. In case 1, culture results showed positive growth of *Mycobacterium bovis*, BCG strain. The results of special stains for fungi were negative in all patients. Culture results from cases 3 and 4 were negative. In cases 2, 3, and 4 there was no family history of tuberculosis and no history of contact with persons having or suspected to have tuberculosis. Table II summarizes the clinical and pathologic findings of patients with BCGitis.

All patients were treated with antituberculous therapy (isoniazid, streptomycin, and rifampin [rifampicin]) for 6 to 9 months. During follow-up periods ranging from 30 to 84 months, 3 patients (cases 1, 3, and 4) were alive and well. No follow-up information was available for case 2.

The 5 patients with suppressed immunity (cases 5-9) had severe combined immunodeficiency disease. All patients had generalized maculopapular skin rash and skin nodules when first examined. All had 1 or more biopsy specimens from the skin nodules in which the microscopic features were similar.
The predominant involvement was in the deep part of the dermis and the subcutaneous tissue. The epidermis and papillary dermis were largely unaffected. Image 2. There were diffuse infiltrates composed of large numbers of histio-
cytes with plump oval nuclei intermixed with neutrophils. Image 3. The histiocytes had abundant gray cytoplasm packed with thin rod-like structures, which can be noted on H&E-stained sections as negatively stained thin rods. Well-
formed granulomas, giant cells, and caseous necrosis were not seen in any of these biopsy specimens, except for a second skin biopsy from case 5, which revealed multiple epithelioid granulomas but no giant cells or caseous necrosis.

Ziehl-Neelsen stain for acid-fast bacilli showed a large number of bacilli within the cytoplasm of the histiocytes, which corresponds to the gray rod-like structures seen on H&E Image 4. Special stains for fungi were negative in all cases. Culture results from all cases (cases 5-9) showed growth of acid-fast bacilli, which were identified to be *Mycobacterium*, bovine type, similar to the strain used in the BCG vaccine.

Table 1 summarizes the clinical and pathologic findings of patients with disseminated BCG infection. All patients were treated with bone marrow transplantation and antituber-
culous therapy, which in this group of patients included isoniazid, rifampin, clarithromycin, and amikacin, and all were alive and well (follow-up range, 48-60 months).

**Discussion**

Postvaccination BCG infections can be divided into 2 major groups with different clinical and pathologic
features. The first, occurring in immunocompetent persons, includes enlargement of regional lymph nodes, with or without suppuration, subcutaneous abscesses at the vaccination site, osteomyelitis, arthritis, and hepatic granulomas. This type, called BCGitis, also can manifest as papular or papulopustular skin lesions. The second type of disease occurs in persons with altered or abnormal immune responses and usually leads to disseminated disease that can be fatal and requires prompt antituberculous chemotherapy and correction of the immunologic status. Another type of disseminated BCG infection, idiopathic disseminated BCG infection, has been reported in children with no apparent immunodeficiencies.

The microscopic appearance of BCG lymphadenitis and BCGitis in general does not differ from tuberculous lymphadenitis. Biopsy specimens from affected lymph nodes and vaccination sites demonstrate multiple epithelioid granulomas and Langhans giant cells. Caseous necrosis is not found commonly, in contrast with tuberculous lymphadenitis. In cases of suppuration, this granulomatous inflammation is intermixed with a large number of neutrophils with abscess formation. Acid-fast bacilli can be demonstrated in some cases, and they can be recovered by culturing suppurative material on Löwenstein-Jensen media. The reported treatment of patients with postvaccination BCG lymphadenitis and BCGitis ranges from no therapy for patients with nonsuppurative lymphadenitis to surgical excision of the suppurative lymph node, followed by spontaneous healing. Some authors recommend the use of antituberculous therapy. The prognosis is excellent, and response to antituberculous drugs is the rule.

The most common pattern of pathologic reaction in disseminated BCG infection associated with immunodeficiencies is diffuse proliferation of histiocytes with plump nuclei intermixed with variable numbers of neutrophils. The cytoplasm of these histiocytes is full of grayish, short, filamentous structures that can be demonstrated on H&E-stained sections and proved to be acid-fast bacilli by Ziehl-Neelsen staining. Well-formed epithelioid granulomas, caseous necrosis, and Langhans giant cells are absent in most of the cases.
In patients with skin nodules, the deep part of the dermis and the subcutaneous tissue are the parts primarily involved, as revealed by the biopsy, and the epidermis and upper half of the dermis are largely unaffected. Another uncommon pattern of reaction in patients with disseminated BCG infection associated with immunodeficiency is formation of epithelioid granulomas with a few Langhans giant cells; such cases show scant acid-fast bacilli on Ziehl-Neelsen stain. The differences in pathologic reaction in this group might be related to the type of immunodeficiency and the patient’s immune status at the time of the biopsy.8

Disseminated BCG infection is considered to result from impaired immunity. However, in half of the cases reported in the literature, regarded as idiopathic, no well-defined immunodeficiency condition could account for the disease.13 Sixteen cases of idiopathic disseminated BCG infection were reported from a national retrospective study in France.13 The minimal prevalence rate was 0.59 per 1 million of vaccinated children. The outcome was poor, with a death rate of 50%.10 Emile et al13 reported 14 cases of idiopathic disseminated BCG infection (collected from the same national retrospective study in France). They compared the pathologic findings of idiopathic disseminated BCG infection with disseminated BCG infection in 22 cases reported in the world literature as individual case reports. They found that 64% (9/14) of the patients with idiopathic disseminated BCG had well-formed (tuberculoid) granulomas, which they called type I, and 59% (13/22) of patients reported in the literature had the diffuse lepromatous-like granulomas, which they called type II, with morphologic features similar to those of the immunocompromised patients in the present study.

The findings by Emile et al13 and noted in a review of the literature8 indicate the type of granuloma formation correlated well with outcome for the patients. Patients with type I granuloma (tuberculoid) had a better overall survival rate than patients with type II granuloma (diffuse lepromatous).13 All 16 patients with idiopathic disseminated BCG infection described by Casanova et al10 were treated with antituberculous therapy and other antibiotics. The overall survival rate was 50%.10 The survival rate for patients in the present study with disseminated BCG infection who underwent bone marrow transplantation and received antituberculous medications was 100%. The difference in the survival rate between the previous studies and the present study emphasizes the importance of treating the immunodeficiency state by bone marrow transplantation or by giving transfer factor in addition to the antituberculous medications.2, 4 However, a fatal outcome has been reported in several cases.2, 4, 11

Table 2 summarizes the relationship among the histologic pattern, type of treatment, and outcome for patients with disseminated BCG infection from different series.

The pattern of postvaccination BCG infection differs clinically and pathologically based on the immunologic status of the patients. Patients with normal immunity have enlarged regional lymph nodes and abscess at the vaccination site (BCGitis). The microscopic appearance is similar to tuberculous lymphadenitis, showing multiple epithelioid granulomas with or without caseous necrosis. Patients with disseminated BCG infection associated with immunodeficiency usually have generalized skin rash and skin nodules. Skin biopsies reveal diffuse (lepromatous-like) infiltrate of histiocytes and, often, polymorphonuclear cells. The histiocytes have abundant gray cytoplasm, which is packed with acid-fast bacilli. Another pattern of pathologic reaction resembles tuberculous granulomas with ill-defined epithelioid granulomas and giant cells. Acid-fast bacilli are absent or rare in the latter type.

The prognosis for patients with BCG lymphadenitis and BCGitis is excellent. In patients with disseminated BCG infection, correction of the immunologic status and antituberculous drugs are the treatments of choice. The response to this combination usually is good; however, fatal outcome has been reported in several cases.

| Table 2 | Relation Among Type of Granulomatous Reaction, Mode of Therapy, and Outcome for Patients With Disseminated Bacille Calmette-Guérin (BCG) Infection From Different Series |
| --- | --- | --- |
| Type of Granuloma | Outcome* |
| No. of Patients | I | II | Both | Type of Treatment | I | II | Both |
| Idiopathic disseminated BCG infection reported from a national study in France13 | 14 | 9 | 4 | 1 | ATT | 78 | 0 | 0 |
| Disseminated BCG infection from individual case reports in the literature13 | 22 | 6 | 13 | 3 | ATT | 67 | 8 | 67 |
| Present study | 5 | 0 | 4 | 1 | ATT and bone marrow transplantation | — | 100 | 100 |

ATT, antituberculous treatment.
* The outcome is the percentage of patients who survived. Type I granuloma is tuberculoid; type II, diffuse lepromatous.

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From the Department of Pathology, King Khalid University Hospital, Riyadh, Kingdom of Saudi Arabia.

Address reprint requests to Dr Al-Bhlal: Dept of Pathology (32), King Khalid University Hospital, PO Box 2925, Riyadh-11461, Kingdom of Saudi Arabia.

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