PRESUMED SYSTEMIC BACILLE CALMETTE-GUÉRIN DISEASE AFTER BCG VACCINATION: REPORT OF A CLINICAL CASE

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Abstract- BCG (bacille Calmette–Guérin) vaccine is administered worldwide to prevent severe forms of tuberculosis. It is considered to be safe; however, occasional complications are seen. The most serious complication is BCGosis. We report a case of BCGosis with granulomatous hepatitis and acid-fast bacilli in liver and spleen. We treated the patient with antituberculosis drugs without any response to treatment.

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INTRODUCTION

Today, BCG (bacille Calmette–Guérin) vaccine is administered worldwide to prevent severe forms of tuberculosis and is recommended for routine use at birth in Iran and countries with high tuberculosis prevalence. It is considered to have an excellent safety profile with rare serious complications (1). The local tissue response begins 2 to 3 weeks after vaccination. Side effects-most commonly, ulceration at the vaccination site and regional lymphadenitis-occur in < 1% to 10% of vaccinated individuals (2). Some vaccine strains have caused osteomyelitis in 1 case per million doses administered (2, 3).

Disseminated BCG infection, so called BCGosis and death have occurred in 1 to ~20 cases per 10 million doses administered, although this problem is restricted almost exclusively to persons with impaired immunity, such as children with severe combined immunodeficiency disease (SCID), chronic granulomatous disease (CGD) or adults with human immunodeficiency virus (HIV) infection (2, 4, 5).

In this article, we are reporting a presumed clinical case of systemic BCG infection or BCGosis referred to Children's Medical Center, affiliated to Tehran University of Medical Sciences.

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CASE REPORT

A 4-month-old male infant was referred to our hospital because of suppurative lymphadenitis in right axillary area, gradually fistulizing, from two months earlier following BCG vaccination at birth. One month prior to admission, the child developed abdominal distension, gastrointestinal (GI) bleeding and progressive jaundice. There was no history of exposure to patients with tuberculosis.

At the time of admission, the child had an axillary temperature of 38.9 °C. He appeared icteric and listless. In physical examination, ascites and

hepatosplenomegaly was detected. Laboratory investigations revealed leukocytosis, anemia, thrombocytopenia, raised erythrocyte sedimentation rate (ESR, 110 mm/hour), profoundly impaired prothrombin time (PT), partial thromboplastin time (PTT), and liver function tests. The child failed to respond to treatment with empirical antibiotic therapy (vancomycin and ceftazidime).

A presumptive diagnosis of disseminated tuberculosis was made and therapy with isoniazid, rifampin and ethambutol started. The infant remained febrile and GI bleeding persisted. After some days the level of consciousness decreased, and at last he died in the third week of therapy.

Necropsy showed diffuse lymphadenopathy, and caseous granulomas and acid-fast bacilli were seen in the liver and spleen (Fig 1). Unfortunately, there was no opportunity to evaluate the patient for immunodeficiency diseases.

We obtained informed consent from our patient's parents to publish details of this case.

DISCUSSION

The live attenuated *Mycobacterium bovis*-derived vaccine was first introduced in 1921. Since then billions of doses have been used and it is historically proven to be safe (1).

However, serious complications (*i.e.* disseminated BCG infection, called BCGosis) rarely do occur. There is a wide variety of complications following BCG vaccination from a simple lymphadenitis in inoculation area to the life-threatening disseminated disease (2, 4, 6, 7).

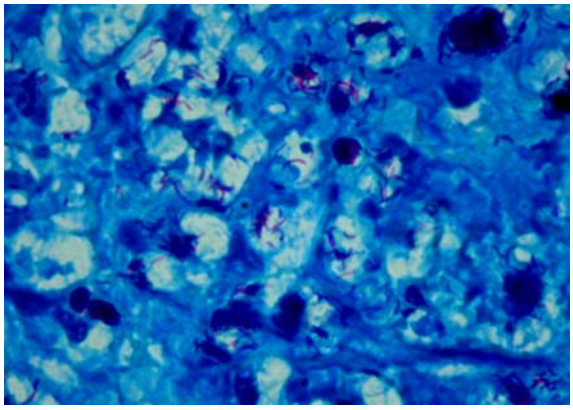

Fig. 1. Acid fast bacilli in liver, ×1000 magnification.

Disseminated BCG infection is found in 1 to nearly 20 cases per 10 million doses, given a mortality rate of 50% to 80%, based on various studies (2, 4, 8). A rise in incidence and mortality rates is seen by time with higher rates in more recent studies, perhaps owing to acquired immunodeficiency syndrome (AIDS) epidemics and its increasing role in immunodeficiency states (4, 5, 8-10). In a review study of 28 cases by Talbot *et al.*, 82% of the cases occurred in children younger than 3 years old and 68% of the patients were male (5). Our patient also was a 4-month-old male infant. Although serious complications of BCG vaccination including generalized lymphadenitis and disseminated infection do occur in normal hosts, these complications are exceptional. Unfortunately, we did not have the chance to evaluate immunodeficiency in our patient. Eighty-six percent of the cases in the Talbot *et al.* study were associated with an immunodeficiency disease of which 38% were AIDS. Immunodeficiency diseases other than AIDS included SCID (20%), CGD (12%), and unidentified cell-mediated immune defects (30%). Response to therapy in immunocompromised patients was poor (17% vs. 100% among patients without an identified immunodeficiency). All of the patients who died were immunodeficient (5).

There are no statistics available in Iran regarding incidence rates of BCGosis among vaccinated children; but since many infants in this country are BCG-vaccinated, we think the incidence rate is high.

In the review study of 28 cases by Talbot *et al.*, it was shown that the most common sites of dissemination, established by culture or histological demonstration of acid-fast bacilli, were lymph nodes, identified in 85% of cases (5). Blood and bone marrow were positive for BCG in one third of cases. Other common sites of dissemination were lungs, liver, spleen, skin and bone. The most commonly reported symptoms were fever, lymphadenopathy and weight loss. Failure to thrive and organomegaly were also common. Our patient was admitted with fever, lymphadenopathy and hepatosplenomegaly. In

necropsy we found acid-fast bacilli in liver and spleen too. Tuberculin test in disseminated BCG infection is often negative.

Talbot *et al.* have developed a working definition of disseminated BCG disease (5). This definition requires the following criteria: 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. Suspicion to disseminated BCG infection is often based on history (especially history of BCG vaccination at birth) and physical examination. Several validated methods for definitive identification of BCG exist among which polymerase chain reaction (PCR) is the least expensive and easiest to perform method (5). Since prompt diagnosis and treatment plays a critical role in outcome of the disease, performing this method as an early definite diagnosis seems necessary.

Information available on useful regimens in the treatment of disseminated BCG infection due to vaccination is limited. Isoniazid, rifampin and erythromycin have been used in the treatment of suppurative lymphadenitis at the site of BCG vaccination (5). Based on several studies (5, 9), nearly all patients with non-BCG strains of *M. bovis* infections responded to therapy with first-line antituberculous agents, including isoniazid, rifampin and ethambutol (except pyrazinamide). Unfortunately, our patient showed no response to this therapy.

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