Disseminated BCG Infection in Severe Combined Immunodeficiency

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The BCG vaccination is generally administered during the newborn period as a routine immunization. Severe complications are rare, but individuals with immunodeficiency are at great risk for developing disseminated mycobacterial infection after BCG vaccination (1).

CASE REPORT

A one-year-old Japanese boy presented with a 6-month-history of nodular eruptions on his trunk. He had been vaccinated with BCG at the age of three months. At the age of eight months, he developed persistent fever. Extensive examinations revealed that the patient suffered from severe combined immunodeficiency (SCID) (T-cell$^-$, B-cell$^+$, NK-cell$^-$ type). On admission, there were numerous dark-red dermal and subcutaneous nodules over the entire body (Fig. 1A). No ulceration was observed at the BCG vaccination site (Fig. 1B). Laboratory findings were as follows: white blood cell count, 16,200/μl (neutrophils 71%, lymphocytes 20%); C-reactive protein, 2.95 mg/dl; AST, 52 U/l; IgG, 965 mg/dl; IgM, 19 mg/dl; and IgA, 2 mg/dl. Blood lymphocyte populations consisted of 3% T cells and 92% B cells, as detected by flow cytometric analysis with CD3 and CD19/CD20 staining. NK-cell activity was below the detection limit, while both bactericidal and phagocytic activity of neutrophils were normal. Histopathologically, there was a dense and diffuse cellular infiltrate mainly comprising histiocytes (Fig. 2A, B). These cells were positive for CD68. Neither multinucleated giant cells nor caseation necrosis was observed. QuantiFeron-TB Gold test was not interpretable because of low responsiveness to a positive control stimulus. Initially, non-Langerhans' cell histiocytosis was suspected, but Ziehl-Nielsen staining revealed numerous bacilli in skin lesions (Fig. 2C). *Mycobacterium tuberculosis complex* was isolated from bacterial cultures of skin and gastric juices, and was confirmed as *M. bovis* BCG strain by PCR analysis (2). Chest X-ray showed multiple nodular shadows in the lung, but no involvement of other organs, such as bone and lymph nodes, was detected. The patient was diagnosed as having disseminated BCG infection and was treated with isoniazid, which resulted in transient improvement in skin lesions. However, after umbilical cord blood transplantation for SCID, skin lesions recurred and he underwent additional anti-tuberculoid therapy with isoniazid, rifampicin, cycloserine and amikacin sulfate. Symptoms showed partial improvement, but complete remission has not been obtained.

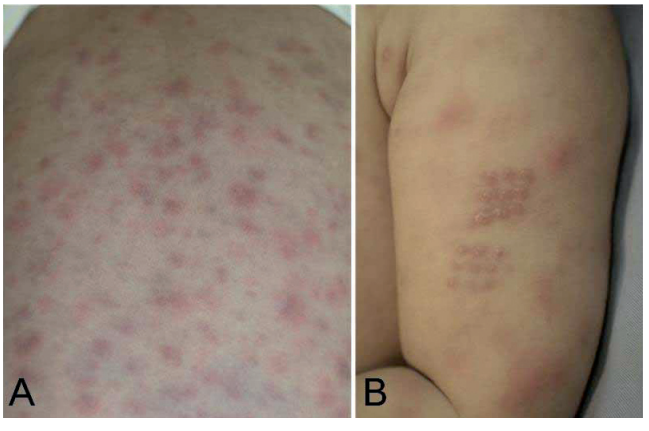

Fig. 1. Clinical features of skin lesions. A: Numerous dark-red subcutaneous nodules on the trunk. B: BCG vaccination site. Ulceration is not observed.

DISCUSSION

Disseminated BCG infection is frequently associated with a deficiency in cell-mediated immunity, such as HIV infection, SCID and chronic granulomatous disease (1, 3–5). BCG vaccination is contraindicated with infants with immunodeficiency, but these individuals are usually inoculated with BCG prior to diagnosis of immunodeficiency, as BCG is administered during the newborn period.

Patients with disseminated BCG infection occasionally present with cutaneous lesions as initial symptoms. These include multiple papulo-nodular or subcutaneous nodular lesions (1, 3–8). Histopathological features are characterized by diffuse histiocytic infiltrates without caseation necrosis or apparent epithelioid granuloma formation (1, 5, 6). Thus, there could be a risk that these patients are misdiagnosed as having histiocytic neoplasms (1, 5, 6), such as Langerhans' histiocytosis and non-Langerhans' cell histiocytosis. The presence of neutrophils may be a useful feature for histopathological differential diagnosis, and in contrast to ordinary tuberculoid lesions, numerous acid-fast bacilli can be detected (1, 3–7). In SCID patients, QuantiFeron-TB Gold test may not be useful for detecting mycobacterial infections due to dysfunction of cell-mediated immunity. Moreover, individuals infected BCG vaccine strain are not detectable by QuantiFeron-TB Gold test.

Disseminated BCG infection in infants with SCID is associated with high mortality. The present case showed a transient improvement with isoniazid therapy and

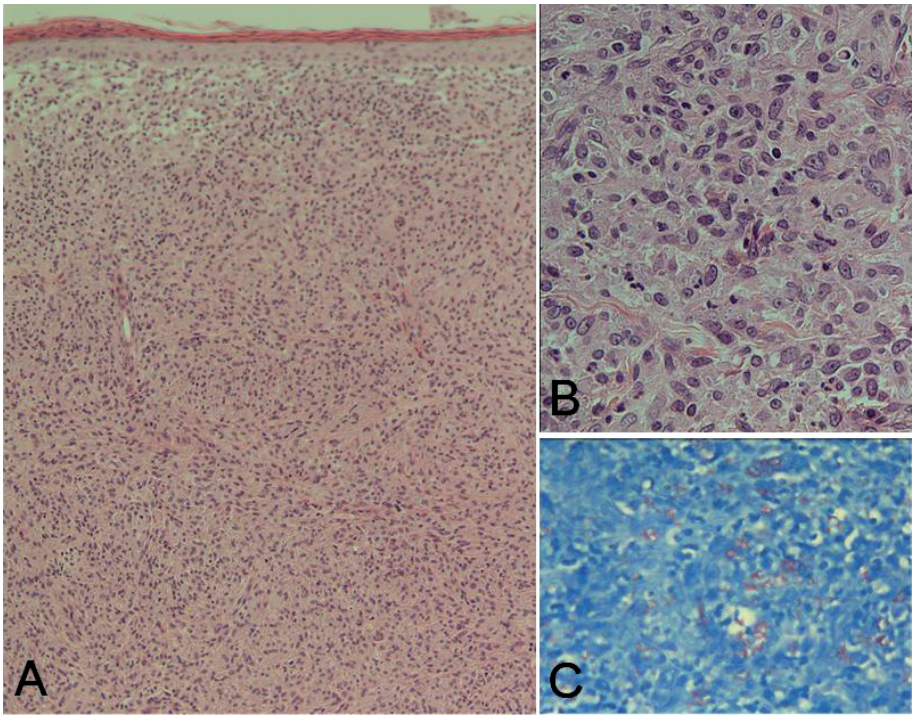

Fig. 2. Histopathological features. Diffuse cellular infiltrates are observed over the entire dermis (H&E, ×40). B: Infiltrative cells largely consisted of histiocytic cells mixed with a small number of lymphocytes and neutrophils (H&E, ×400). C: Ziehl-Nielsen staining. Numerous acid-fast bacilli are detected.

received umbilical cord blood transplantation. Notably, however, skin lesions recurred after umbilical cord blood transplantation. This may be due to restored immune function against *mycobacterium* by cord blood transplantation, i.e., immune reconstitution syndrome, as observed in HIV-infected patients with tuberculosis during anti-retroviral treatment, although the immune reconstitution syndrome is usually characterized by severe systemic responses, such as fever, lymphadenitis, pulmonary infiltrates (9, 10).

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The authors declare no conflict of interest.

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