

LETTER TO THE EDITOR

Tuberculous granuloma developed 9 years after bacillus Calmette–Guérin vaccination in a patient with immunodeficiency

Dear Editor,

The bacillus Calmette–Guérin (BCG) vaccine has a safety profile¹ and is administered to newborns as a routine immunization in Japan. We report a case of tuberculous granuloma resulting from BCG vaccination in a patient with immunodeficiency.

An 11-year-old Japanese girl was referred to our department. She noticed nodular eruptions on her left upper arm, lower eyelid and right chest (near the axilla) from 9 years old (Fig. 1a–d). Ulceration was not observed at the BCG vaccination site (Fig. 1d).

At 5 months after birth, she was administered the BCG vaccine. At 10 months after birth, lymphadenitis of the left axillary developed, a pus culture was positive for BCG bacterium and she was noted to have hypogammaglobulinemia. At 6 years old, she developed toxoplasmic encephalitis, right cervical lymphadenitis and erythema nodosum. Nothing was remarkable in her family medical history.

A skin biopsy of her left upper arm revealed a dense granuloma of lymphocytes and epithelial cells in the subcutaneous tissue from the lower dermis (Fig. 1g). Periodic acid–Schiff and Ziehl–Neelsen stainings did not reveal bacilli. Laboratory findings were as follows (normal ranges): white blood cell count, 9280/μL; neutrophils, 54%; lymphocytes, 29%; T cells, 81% (59–88%); B cells, 11% (4–26%); CD4, 47% (30–55%); CD8, 30% (17–44%); natural killer cells, 7% (7–28%); lymphocyte blast transformation test, stimulation index (SI, phytohemagglutinin), 573.5 (101.6–2643.8); SI (concanavalin A), 539.1 (74.7–1793.2); immunoglobulin (Ig)G, 419 mg/dL (870–1700); IgM, 15 mg/dL (110–410); IgA, 14 mg/dL (46–260); and IgE 3 IU/mL (0–232). T-SPOT.TB (Oxford Immunotec, Abingdon, UK), bacterial/fungal culture and polymerase chain reaction (PCR) tests for *Mycobacterium tuberculosis*, *Mycobacterium avium* and *Mycobacterium intracellulare* were negative.

After 5 weeks, an *M. tuberculosis* complex was isolated from bacterial cultures of the skin and confirmed as the *Mycobacterium bovis* BCG Tokyo 172 strain through PCR analysis (Fig. 1h).² Tuberculin reactivity was strongly positive. No other organ involvement was detected through computerized tomography. Her nodular eruptions improved impalpably after 6 months antituberculosis medications (isoniazid, rifampicin). The most likely diagnosis was common variable

immunodeficiency, and she was suspected of having a defect of innate immunity or phagocytic function in addition to antibody deficiencies; therefore, we are planning to perform a genetic analysis to confirm a diagnosis.

The reported prevalence of BCG complications varies.^{3–5} In the USA, more than 200 cases of disseminated BCG infection occurred in children with primary immunodeficiency disease. In Europe, BCG complications occur in 4.2 for every million vaccinations.⁴ In Japan, this incidence was 11.8 for every million from 2003 to 2005.⁵ To our knowledge, 26 cases of tuberculosis granuloma were reported in Japan (1983–2017). These cases were administered the BCG vaccine at the ages of 3–10 months (mean age, 4.5). The period from BCG inoculation to rash appearance was 2–24 months, and the majority of rashes appeared within 2–4 months after BCG inoculation. Six patients improved without antituberculosis drugs or resection, and six cases were identified as *M. bovis* BCG.

Bacillus Calmette–Guérin vaccination is contraindicated in infants with immunodeficiency, but they are vaccinated prior to diagnosis. They may present with cutaneous lesions as initial symptoms, and BCG infection should be considered as a differential diagnosis.

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CONFLICT OF INTEREST: None declared.

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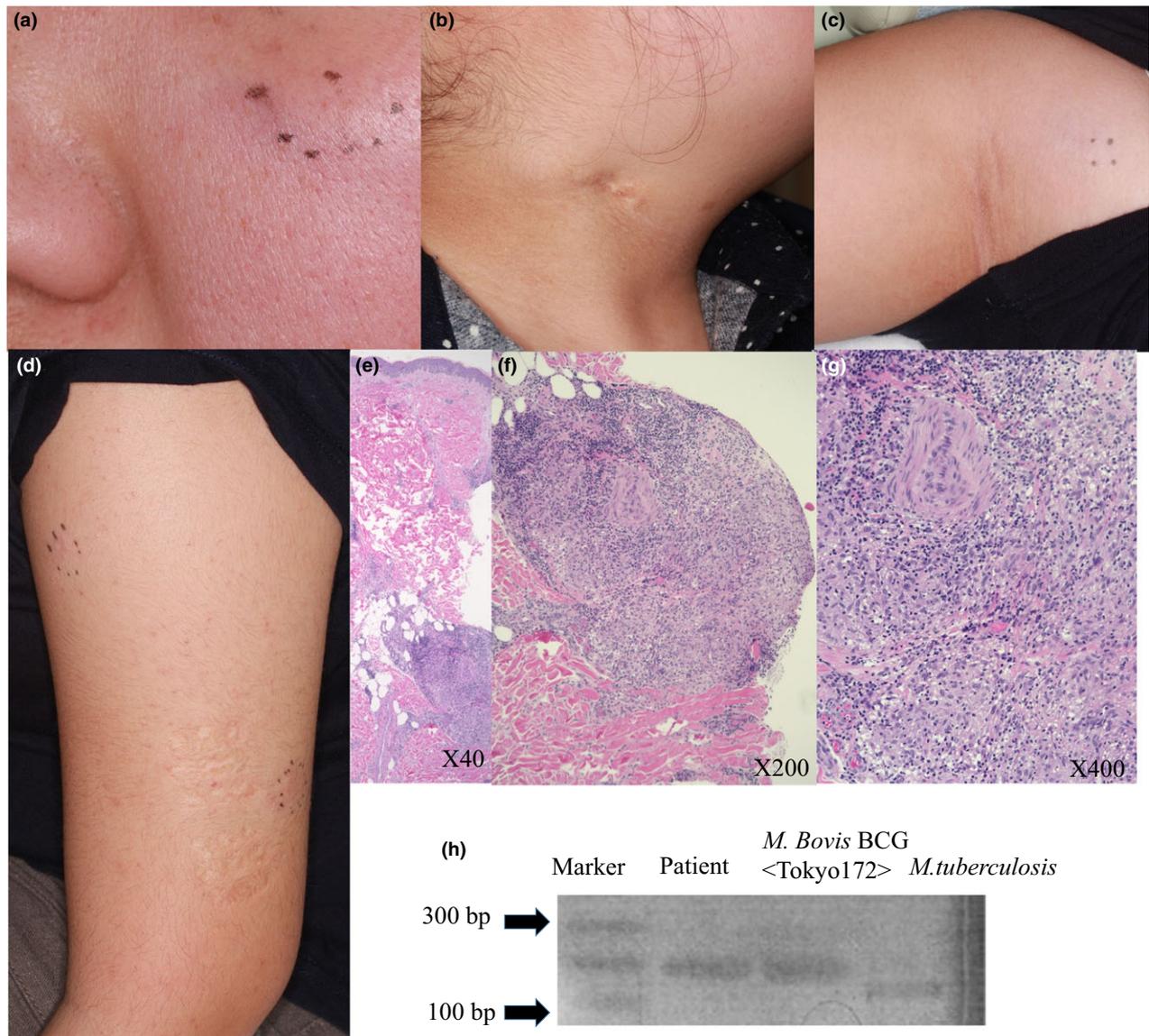


Figure 1. Clinical features of the skin lesions. Nodular eruptions on (a) the lower eyelid, (b) cervical lesion, (c) right chest, (d) biopsy site and bacillus Calmette–Guérin (BCG) vaccination site of the left upper arm. (e) The specimen showed a dense granuloma of lymphocytes and epithelial cells in the subcutaneous tissue from the lower dermis (hematoxylin–eosin [HE]). (f,g) Additionally, there were many large nucleus cells and an inflammatory cell with lymphocyte infiltration (HE). (h) Polymerase chain reaction confirmed *Mycobacterium bovis* BCG Tokyo 172. bp, base pairs.

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