

A rare case of primary inoculation tuberculosis seen after varicella

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Primary inoculation tuberculosis (TB) is a rare form of cutaneous TB resulting from direct introduction of *Mycobacterium tuberculosis* into the skin or mucosa of a previously uninfected, nonimmune person. We herein report the first case, to our knowledge, of primary inoculation TB to be seen after varicella; this case explains the possible mechanism of varicella-zoster virus-mediated transient cellular immune suppression that predisposed the patient to cutaneous TB. In this case, we believe that varicella-zoster virus (VZV) infection predisposed the patient to primary inoculation TB by leading to direct inoculation of tuberculosis bacilli through vesicles or by suppressing cellular immunity.

Key words: *Mycobacterium tuberculosis*, primary inoculation tuberculosis, varicella.

Cutaneous tuberculosis (TB) is a relatively uncommon manifestation of TB, accounting for only 1–2% of all cases.¹ *Mycobacterium tuberculosis* is the predominant causative organism of cutaneous TB. Occasionally, *Mycobacterium bovis* and the bacillus Calmette-Guérin (BCG), an attenuated form of *M. bovis*, have also been associated with the development of cutaneous lesions.² The clinical presentation is determined by the outcome of the host immune response, the mycobacterial virulence and the route of entry of the bacilli.^{1,2}

Primary inoculation tuberculosis, also known as tuberculous chancre or primary tuberculous complex, is a rare form of cutaneous TB that results from the direct introduction of the organism into the skin or mucosa of a non-sensitized individual.³ Here, we describe a rare case of primary inoculation TB following varicella in an otherwise healthy boy and also explain the mechanism of varicella-zoster virus (VZV)-induced cellular immunosuppression that might be a cause for development of cutaneous TB in this patient.

Case Report

A 14-month-old, otherwise healthy boy

presented with a 3-week history of a painless swelling located on the left anterior chest wall, 3 cm below the left nipple. There was no history of trauma or injury; however, he had suffered from varicella one month prior to the beginning of the lesion. Varicella was diagnosed by a pediatrician; the patient had not been immunized against varicella. Physical examination revealed an ulcerative nodular lesion, approximately 3 cm in diameter, located on the left anterior chest wall. The patient was afebrile, and there was no regional lymphadenopathy. Initial laboratory studies disclosed normal values for complete blood cell count, erythrocyte sedimentation rate and C-reactive protein. Indicative of past infection, serum VZV IgM titer by ELISA was negative, and VZV IgG titer was positive. The chest X-ray was normal. The lesion was totally excised, and histopathological analysis showed a granulomatous infiltrate with central caseation necrosis and giant cells of the Langhans type, including the presence of acid-fast bacilli (Fig. 1). Although culture of the biopsy specimen was negative, a polymerase chain reaction (PCR) test revealed the presence of *M. tuberculosis*. These clinical and histopathological findings,

along with the positivity of PCR for *M. tuberculosis*, established a diagnosis of primary inoculation TB. The patient had received BCG vaccination at 2 months of age; there was no history of exposure or tuberculosis infection in his family. All close contacts (household members and grandparents) were screened for TB, and all investigations concerning the source of the infection had normal findings. Results of the tuberculin skin test and interferon (IFN)- γ release assay-the QuantiFERON-TB Gold test-were found to be negative. Serological testing for human immunodeficiency virus was non-reactive. Anti-tuberculosis treatment with a combination of isoniazid, rifampin and pyrazinamide was given for the first 2 months, followed by isoniazid and rifampin for an additional 4 months. The patient recovered, with no relapse after 6 months of standard tuberculosis treatment. During follow-up, all immunological investigations had normal findings, including peripheral blood lymphocyte subsets, in vitro lymphoproliferative response to mitogens, serum IgG, IgA and IgM levels, flow cytometric analysis of interleukin (IL)-12R β 1 cell surface expression on activated T cells, and IFN- γ cell surface expression on monocytes.

Discussion

Cutaneous tuberculosis has a worldwide distribution; it constitutes a small portion of all cases of extrapulmonary tuberculosis.¹ Primary inoculation TB is an exogenous infection, which is caused by the direct inoculation of tuberculosis bacilli into a traumatized area of the skin or mucosa of a non-sensitized host who lacks natural or acquired immunity. The disorder generally occurs as an occupational disease in healthcare workers. It can also occur in children with no previous BCG vaccination and a history of exposure to *M. tuberculosis* through a household member or caregiver with pulmonary TB in endemic areas.³ The present case was living in endemic area but had been vaccinated with BCG at 2 months of age, and there was no known history of exposure to the bacilli or tuberculosis infection in his family. Our initial impression of BCG-related skin involvement was excluded by the positive result of PCR for *M. tuberculosis* in this patient.

The skin lesion in cutaneous TB develops 2-4 weeks after inoculation, and regional lymph nodes may become infected 3-8 weeks later. The skin lesion and the affected regional

lymph node constitute the tuberculous primary complex of the skin that is analogous to the Ghon's complex of pulmonary TB infection.¹ The initial lesion begins as a reddish-brown papule or nodule that gradually enlarges to form a painless, shallow, firm, sharply demarcated ulcer. Skin lesions are usually 1 cm or less in diameter, but can occasionally exceed 5 cm. The face, extremities and genitals are the most common sites for lesion development. Conjunctival, gingival and palatal involvement has also been reported. Fever and systemic reactions are generally minimal.^{1,2} The skin lesion that was seen in our patient, however, was located on the left anterior chest wall, without any regional lymph node. This is not a common site of predilection and manifestation of the disease.

In this case, we believe that VZV infection predisposed the patient to primary inoculation TB because of direct inoculation of tuberculosis bacilli through the vesicles or suppressed cellular immunity. Minor cuts, trauma or pyoderma resulting in compromised skin or a compromised mucosal barrier usually precede the infection, as *M. tuberculosis* cannot penetrate intact skin.^{1,2} After invasion of the skin, the mycobacteria either proliferate intracellularly within macrophages, leading to progressive disease, or are controlled by the host immune reaction.² Adversely, key factors required for cellular immune response against TB are down-regulated by VZV infection through the mechanisms that have been shown in previous reports.⁴⁻⁷

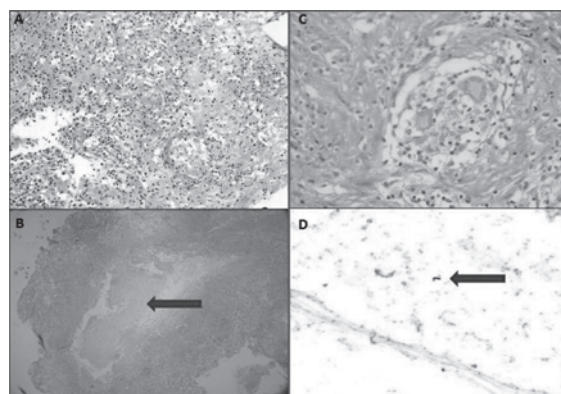


Fig. 1. Histopathological analysis of the nodular lesion showed (A) a granulomatous infiltrate with (B) central caseation necrosis (arrow), (H&E stain, 40X) and (C) giant cells of the Langhans type, (H&E stain, 200X), including (D) the presence of acid-fast bacilli (arrow) (Kinyoun staining, 1000X). H&E=hematoxylin and eosin.

The role of cellular immunity is important in the protective response against *M. tuberculosis*. Mechanisms of protective immunity that have been investigated in mouse models have demonstrated that both major histocompatibility complex (MHC) class I- and class II-restricted T cells contribute to immunity against TB. MHC class II-restricted CD4+ T cells are key antimycobacterial components of the adaptive immune response in controlling TB infection, and MHC class I-restricted CD8+ T cells contribute to protective immunity against *M. tuberculosis* by recognizing and lysing infected cells and killing the intracellular bacteria.⁸

According to previous reports,^{4,7} VZV infection can cause transient depression of cell-mediated immunity during the acute phase of the illness manifested by decreased CD4+ T-lymphocytes, increased suppressor CD8+ T-lymphocytes and decreased in vitro proliferation with phytohemagglutinin and tuberculin purified protein derivative. In a prospective study of children with varicella infection,⁶ significant changes in T-lymphocyte subsets during the acute phase of infection, including a decrease in CD4+ T-cells and an increase in CD8+ T-cells, which were normalized one month later, were reported. It was also demonstrated that VZV infection inhibited both MHC class I and class II expressions in human fibroblasts, and it was suggested that these effects might transiently protect VZV-infected cells from CD4+ T-cell immune surveillance as well as prevent recognition of the infected cells by cytotoxic CD8+ T cells.^{4,5}

Based on these studies, mechanisms of VZV-induced immunosuppression during the acute phase of the disease include the changes in T-lymphocyte subsets, decreased in vitro proliferation with mitogens and inhibition of MHC class I and class II expressions on infected cells. These changes may explain the immunopathogenesis of infection after *M. tuberculosis* was introduced into the skin. Therefore, we concluded that suppressed cellular immunity due to VZV might have facilitated the development of cutaneous TB in this patient.

Untreated primary inoculation TB lesions heal, with scarring, within approximately 12 months but they may progress to acute miliary TB, or may form lupus vulgaris or scrofuloderma. Therefore, antituberculous medication, which is

the same as that recommended for pulmonary TB, is indicated for cutaneous TB.^{1,2,9} However, ethambutol can be omitted in patients with a low risk of resistance to initial treatment with isoniazid.¹⁰ Surgical interventions can also be useful for treatment of an isolated lesion, as seen in our patient.

In conclusion, primary inoculation TB should be considered in pediatric patients with any painless, non-healing ulcerated skin lesions seen after minor trauma, pyoderma or vesicles, even if the clinical presentation is not typical. It is usually seen in patients with a suppressed immune system due to an underlying disease or infection such as varicella, as was noted in our patient. A high degree of suspicion is needed to avoid misdiagnosis of this rare disease, especially in areas with high TB prevalence, such as our country.

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