Case Report

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Supraclavicular BCG Lymphadenitis Noted at 21 Months after BCG Vaccination Confirmed by a Molecular Method

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Bacille Calmette-Guérin (BCG) lymphadenitis is the most common complication of BCG vaccination. It commonly occurs in infants aged <6 months involving ipsilateral axillary lymph nodes. We described BCG lymphadenitis in a 22-month-old boy presenting swelling of left supraclavicular lymph node that was confirmed by real-time polymerase chain reaction (PCR) and the multiplex PCR targeting the region of difference (RD).

Key Words: BCG lymphadenitis, Tokyo strain

Introduction

Although bacille Calmette-Guérin (BCG) vaccination has been accepted as an effective and safe protective measure against the disseminated disease and meningitis in childhood tuberculosis, various complications have been reported[1]. BCG lymphadenitis is one of the most common complication resulting from this vaccination and mostly presented with ipsilateral axillary lymphadenitis. BCG lymphadenitis may develop as early as two weeks after vaccination and disappear spontaneously within six months[1-3]. These characteristics could help for diagnosis and treatment of BCG lymphadenitis clinically. However, atypical clinical features may make it difficult to differentiate from tuberculous lymphadenitis, which necessitates the identification of the BCG strain with phase typing or gene analysis. We report a boy presenting supraclavicular lymphadenitis at 21 months after BCG Tokyo strain vaccination, which was confirmed by the real-time polymerase chain reaction (PCR) targeting the *senX3-regX* intergenic region (IR) and the multiplex PCR that targeted the region of difference 1 (RD1), RD8 and RD14.

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Case report

A 22-month-old Korean boy presented with localized swelling of left supraclavicular area, which was developed 2 weeks ago, in December 2012. The lesion was developed 2 weeks ago and there was no accompanying symptom such as fever, weight loss, and cough. He was born by cesarean

section delivery with a birth weight of 2.48 kg at full term. The patient had no previous admission or operation history and no known history of contact with tuberculosis patients. He had been vaccinated the BCG Tokyo strain at left upper arm in the multipuncture method at 15 days of age. There was no specific family history except thyroid cancer and hyperthyroidism of his father. He attended a daycare center.

Vital signs included a temperature of 36.5℃, a pulse rate of 100 beats per minute, and a respiratory rate of 24 breaths per minute. Physical examination revealed a 1.5×1.0 cm-sized mass in his left supraclavicular area, which was tender, slightly erythematous, and fluctuant. There was no inflammation on his BCG inoculation site. The laboratory findings were as follows: white blood cell count 15,610/mm^3 with 36% neutrophils and 51% lymphocytes, hemoglobin 13.4 g/dL, platelets 357,000/mm^3, erythrocyte sedimentation rate 6 mm/hr, and C-reactive protein 0.51 mg/dL. Plain radiographs of both clavicles did not show any bony lesion, and the ultrasonography revealed a 1.6×1.2 cm-sized hypoechoic lesion with some internal echogenic foci on the subcutaneous fat layer of the left midclavicular area. One week later, his supraclavicular mass was larger than before (about 2.0×1.5 cm) and still tender, and showed more erythematous change on its overlying skin (Fig. 1). Chest x-ray did not reveal any lung lesion and the result of tuberculin skin test was positive (13 mm) at 48 hours after inoculation of Tuberculin PPD RT 23 SSI (2 T.U.) (Accesspharm, Inc., Seoul, Korea). We performed needle aspiration for the lesion and 2-3 mL of yellowish pus was yielded. On cytopathologic finding of the aspirate, a few histiocytic aggregates, many neutrophils, and some calcified materials in a necrotic background were seen. Acid-fast staining and mycobacterial culture of the aspirate were negative. Other pyogenic bacteria were not found on culture. The results of real-time PCR using AdvanSure TB/NTM real-time PCR Kit (LG Life Science Ltd., Seoul, Korea) were positive for *Mycobacterium tuberculosis* complex and negative for nontuberculous mycobacteria. However, these tests were not helpful in distinguishing BCG strains from other *M. tuberculosis* complex strains. Because the patient had no contact history of tuberculosis and tuberculous lymphadenitis more likely occurred in older children, we needed to distinguish the strain of the mycobacterium to decide an appropriate treatment. The BCG Tokyo strain was confirmed to be the causative mycobacterium by the real-time polymerase chain reaction targeting the *senX3-regX3* IR and the multiplex PCR that targeted RD1, RD8 and RD14, as previously described[4]. He was treated by repeated aspirations without anti-tuberculous medication, and recovered 3 months after the first aspiration.

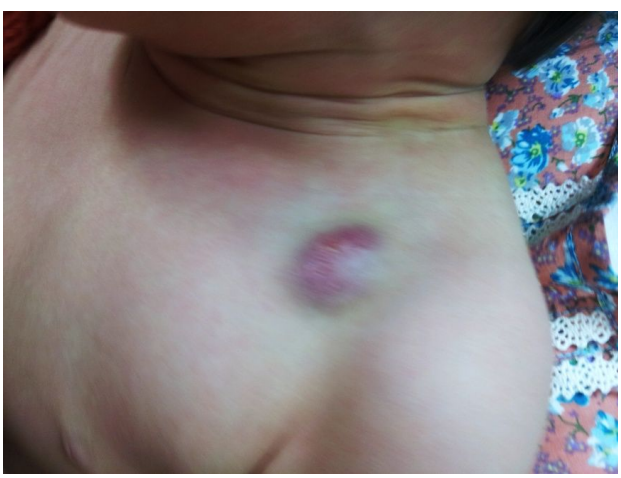

Fig. 1. Erythematous, fluctuant and tender mass on left supraclavicular area presented at 21 months after BCG vaccination.

Discussion

BCG lymphadenitis is a common local reaction of BCG vaccination. Incidence of BCG lymphadenitis varies depending on the vaccine strain, the technique of administration, the age of the recipient, and the dose administered, with the rate ranging from 0.1 to 5 per 1000 vaccinated children[5]. In Korea, the incidence rate of BCG lymphadenitis has been reported 0-6%[6]. There have been reports from many countries with an estimated incidence of <4/10,000 vaccinees younger than 1 year old[7, 8].

After vaccination, the BCG strain starts multiplying rapidly at the site of inoculation and is later transported through the lymphatics to the regional lymph nodes, followed by the hematogenous dissemination of the BCG, resulting in creation of very small foci in different organs. This is called "normal BCG-itis" in the course of successful BCG vaccination[9]. Among these organs, slightly enlarged regional nodes are common after BCG vaccination, but are rarely noticeable unless searched for specifically. This subclinical lymphadenitis regresses spontaneously, is of no practical importance, and may not be regarded as a complication. However, there is no easy way to differentiate "normal" from "abnormal" and there is no agreed definition as to what constitutes BCG lymphadenitis, particularly with regard to the size of lymph node enlargement and its onset after vaccination.

BCG lymphadenitis is usually presented with finding of isolated enlarged axillary lymph nodes ipsilateral to the site of BCG vaccination in the first 5 months after vaccination[7]. The clinical features are usually sufficient for making the diagnosis in the majority of cases. Investigations such as ultrasonography, tuberculin skin test and the cytopathology of the aspirate have limited roles in the diagnosis of BCG lymphadenitis. Because the differential diagnosis with tuberculous lymphadenitis may be difficult, the definitive diagnosis of BCG lymphadenitis can be made by the identification of the BCG strain from the affected focus with phase typing or gene analysis.

The management of regional BCG lymphadenitis is controversial. Since non-suppurative lymphadenitis regresses without any ill effect and suppurative lymphadenitis is associated with an unpleasant and prolonged course, prevention of suppuration becomes the most important objective in the treatment of BCG lymphadenitis. Once suppuration has occurred, prevention of spontaneous discharge and sinus formation should be the next aim. Currently, there are various approaches to BCG lymphadenitis, including observation, anti-tuberculous medication, surgical excision, or aspiration[7].

However, there is no convincing evidence that the use of anti-tuberculous medication either reduces the risk of suppuration or shortens the duration of healing. Surgical excision is definitively not recommended for non-suppurative cases because it requires general anesthesia which carries a risk to young children and infants[10]. In the case of suppuration, surgical treatment either by needle aspiration or by surgical excision could be undertaken. Though surgical excision is likely to be curative and will reduce the healing time, repeated needle aspiration has recently been advocated as not only diagnostic but also therapeutic procedure to avoid suppuration and prolonged drainage[8].

In our case, clinical examination revealed supraclavicular lymphadenitis at 21 months after BCG Tokyo strain vaccination on the ipsilateral side of

the vaccination. Supraclavicular swelling was accordant with suppurative lymphadenitis. The longer interval from vaccination to the onset of the lymphadenitis was different from the typical finding of BCG lymphadenitis, and solitary supraclavicular lesion needed to differentiate from other diseases. Chest x-ray did not reveal any lung lesion and his PPD skin test was positive. The aspirate from the lesion was negative for acid-fast staining and mycobacterial culture. However, the results of real-time PCR were positive for *M. tuberculosis* complex and negative for nontuberculous mycobacteria. These findings can be mistaken for clinical and genetic appearance of tuberculous lymphadenitis.

However, AdvanSure TB/NTM real-time PCR Kit has a high sensitivity (100%) to tuberculosis mycobacteria but a low sensitivity (55.6%) to nontuberculous mycobacteria, which mean that only the PCR method using this kit would not be enough for detecting nontuberculous mycobacteria[11]. In addition, considering that suspected tuberculous lymphadenitis patients without an identifiable tuberculous contact were subject to further investigations for differential diagnosis of M. bovis BCG, we performed the targeted real-time PCR for the RD1, RD8 and RD14[12].

Multiplex PCR method based on genomic RD was developed for the differentiation of *M. canettii, M. tuberculosis, M. africanum, M. microti, M. pinnipedii, M. caprae, M. bovis* and *M. bovis* BCG. The size of the respective multiplex PCR amplification products corresponded to the presence of the different *M. tuberculosis* complex members, enabling us to differentiate different strains belonging to the *M. tuberculosis* complex and making surveillance of species-specific disease suitable[13, 14]. This diagnostic method could help to confirm BCG lymphadenitis. Based on these results, we could treat the patient by repeated aspirations without anti-tuberculous medication.

In conclusion, atypically delayed presentation of BCG lymphadenitis could make the differential diagnosis from tuberculous lymphadenitis difficult. We distinguished between BCG lymphadenitis and tuberculous lymphadenitis via the targeted real-time PCR for the gene of the BCG Tokyo strain. We report this case regarding the diagnostic work-up, differential diagnosis, and treatment with a brief review of the literature.

한 글 요 약

분자생물학적 방법으로 확진한 접종 21개월 후에 발생한 BCG 쇄골상부 림프절염 1례

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BCG 림프절염은 BCG 접종 후에 생기는 가장 흔한 합병증이다. BCG 림프절염은 대부분 6개월 미만의 영아에서 발생하며 접종한 부위와 같은 쪽 겨드랑이 림프절을 침범하는 경우가 많다. 본 저자들은 생후 15일에 Tokyo 주 BCG 백신을 접종한 22개월 남자아이에서 왼쪽 쇄골상부 림프절 부위에 발생한 BCG 림프절염을 경험하여 이에 대해 보고한다. 우리는 림프절 흡인을 시행하여 얻은 검체에서 실시간 중합효소 연쇄반응과 region of difference (RD)에 대한 다중 중합효소연쇄반응으로 *M. bovis* Tokyo 주에 의한 감염을 확인하였고 반복적인 흡인을 통해 치료하였다.

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