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Case Report / Olgu Sunumu

IL-12Rβ1 Deficiency Presenting with BCG Lymphadenitis: A Case Report

BCG Lenfadeniti ile Başvuran Kalıtsal IL-12Rβ1 Eksikliği; Olgu Sunumu

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Abstract: Mendelian susceptibility to mycobacterial disease (MSMD) is a primary immunodeficiency disease characterized by a greater propensity for infection development with weakly-virulent mycobacterial strains and various intracellular pathogens including salmonella. After receiving the Bacille-Calmette-Guérin (BCG) vaccine, patients typically present to clinics with local or widespread mycobacterial infections, recurrent moniliasis, and salmonella infections. The pathogenesis of the disease is caused by a decrease in interferon-gamma production or an inadequate response to interferon-gamma release. The most common genetic deficiency in MSMD is interleukin-12 receptor deficiency. In this report we describe the case of an 11-month-old boy presenting with suppurative lymphadenitis after BCG vaccination who was found to have interleukin-12 receptor β1 deficiency by mutation analysis. We emphasize that MSMD should be investigated in patients who develop local or systemic mycobacterial infections after receiving the BCG vaccine.
Keywords: BCG lymphadenitis, mycobacterial infection, primary immune deficiency

Özet: Mikobakteri enfeksiyonlarına karşı Mendelyan yatkınlık, zayıf virülan mikobakteri suşları ve Salmonella gibi çeşitli hücre içi patojenlere duyarlılık ile karakterize bir primer immün yetmezlik hastalığıdır. Hastalar genellikle Bacille Calmette-Guerin aşısı sonrası gelişen lokal veya yaygın mikobakteri infeksiyonları, tekrarlayan moniliazis ve salmonella infeksiyonları ile kliniklere başvururlar. Hastalığın patogenezinden azalmış interferon gama üretimi yada interferon gamaya yetersiz yanıt sorumludur. İnterlökin-12 reseptör β1 eksikliği mikobakteri enfeksiyonlarına karşı Mendelyan yatkınlıkta en sık görülen genetik eksikliktir. Burada Bacille Calmette-Guerin aşısı sonrası süpüratif lenfadenit gelişen ve mutasyon analizi ile interlökin-12 reseptör β1 defekti saptanan 11 aylık bir olgu sunulmaktadır. Bacille Calmette-Guerin aşısı sonrası gelişen lokal veya sistemik mikobakteri infeksiyonlarında IL-12 reseptör β1 eksikliği göz önünde bulundurulmalıdır.
Anahtar Kelimeler: BCG, IL-12Rβ1, lenfadenit, mikobakter

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1. Introduction

Mendelian susceptibility to mycobacterial disease (MSMD) was clinically defined in the 1950s as a rare disease, and its genetic etiology was discovered in 1996. The pathogenesis of the disease is associated with decreased interferon (IFN) production or insufficient response to its release. A mutation in any of the genes encoding the essential proteins of the type 1 cytokine cascade may lead to the development of this deficiency [1]. So far, nine autosomal (IFNGR1, IFNGR2, IL-12B, IL-12R1, STAT1, IRF8, ISG15, TYK2, and RORC) and two X-linked (NEMO, CYBB) genes have been identified as culprits of MSMD [2-5]. Interleukin (IL) -12 is a cytokine that promotes the production of IFNs from T cells and natural killer cells, which boost immunity against intracellular bacteria, such as *mycobacteria and salmonella*. Therefore, the IL-12/IFN-axis is critical in human immunity against *mycobacteria* [6-7]. In such cases, infections with weakly-virulent non-tuberculosis *mycobacteria and salmonella* strains are possible [8-9]. Following the administration of the Bacille-Calmette-Guérin (BCG) vaccine, various adverse events may occur, ranging from regional reactions (such as lymphadenitis) to disseminated BCG infection [2]. The most common genetic deficiency in MSMD has been identified as IL-12R1 deficiency. We present a case of lymphadenitis development following BCG vaccination and the ensuing investigation of its cause, which ultimately yielded IL-12R1 deficiency–discovered through mutation analysis.

2. Case Report

An 11-month-old girl was brought in with complaints of swelling, redness, and discharge under her left armpit. The BCG vaccine had been applied when she was 2 months old (as per the routine schedule), and the complaints of armpit swelling had developed at 6 months of age. She was given oral antibiotic treatment when she first applied to a healthcare facility, with a diagnosis of acute lymphadenitis, but the symptoms did not improve with said treatment. Our physical examination identified a BCG vaccination scar on the left arm and a 2x2 cm ulcerated, draining, painless lymphadenopathy in the anterior axillary region on the same side (Figure 1). Other system examinations were unremarkable. The tuberculin skin test measured 11 mm of induration. In the laboratory analyses, Hb was 11.3 g/dL, leukocyte count was 9.450 / mm3 (neutrophil 2660 / mm3, lymphocyte 5.830 / mm3) and platelet count was 299.000 / mm3 Other viral and bacterial tests, including Human Immunodeficiency Virus (HIV) were negative. Chest radiography and abdominal ultrasonography revealed no apparent pathologies. The lymph node was biopsied using fine needle aspiration, and acid-resistant bacteria were not found in the biopsy material when stained with Erlich-Ziehl-Nielsen. The polymerase chain reaction for *mycobacterium tuberculosis* was negative, and there was no growth in the culture performed with Löwenstein–Jensen medium. A lymph node histopathological examination revealed several lymphoid tissue fragments and lymphoid cells. Immunoglobulin G, A, M, E levels and immunodeficiency features in lymphocyte subgroups were all within reference ranges for age. Nitroblue tetrazolium (NBT) was normal. A mutation in the IL12R1 gene was discovered with a sequence analysis to assess MSMD (Figure 2). The parents were third-degree consanguineous, and the mother had no known medical history other than Familial Mediterranean Fever. During the patient's six-month follow-up, ulceration and lymphadenopathy in the skin above the lymph node regressed without anti-tuberculosis treatment (Figure 3), and no additional problems were observed.



Figure 1. Ulcerated lymphadenopathy in the anterior axillary region

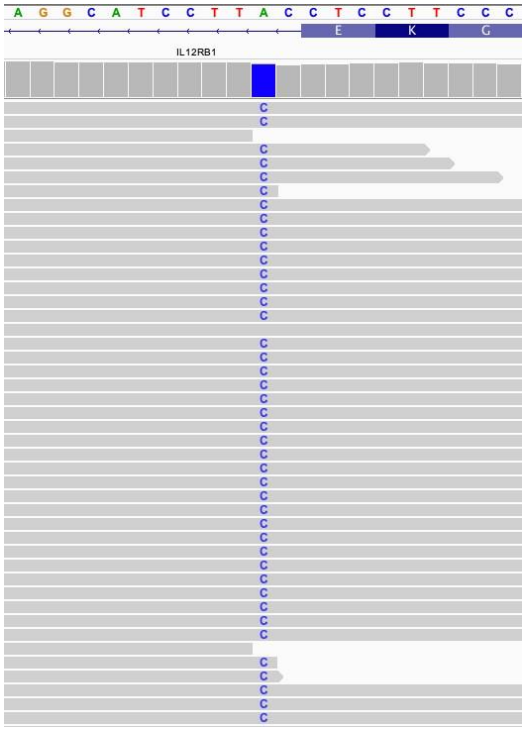


Figure 2. Genetic Sequence Analysis



Figure 3. Post Treatment Picture of Axillary Lymphadenopathy

3. Discussion

The BCG vaccine is one of six vaccines included in the World Health Organization's expanded vaccination program. BCG, the origin of the vaccine, is a *mycobacterial* member of the *mycobacterium tuberculosis* complex. This vaccine is currently being used actively in Turkey, similar to many other countries. It is known that the incidence of significant side effects is very low in individuals with healthy immune systems, barring the relatively higher frequency of local reactions, such as cellulitis, abscess, and rarely, suppurative lymphadenitis. Regional lymphadenitis (BCG-itis) or widespread infection involving lymph nodes, lungs, kidneys, spleen and other organs (BCG-osis) may develop after BCG vaccination in patients with underlying cellular immune deficiency [10]. BCG lymphadenitis is a common development in MSMD patients in countries where the vaccine is administered [6,11]. In a large study of 141 patients with IL-12R1 deficiency from 30 countries, it was discovered that 84 of the 108 patients who had received the BCG vaccine had developed BCG-related infection, with 17 of the cases being local infections [2]. In our case, the BCG vaccine was administered according to the routine vaccination schedule (in the second month), and regional suppurative lymphadenitis developed approximately 4 months after. Infection with *mycobacterium tuberculosis* has been observed in a small number of MSMD patients, as have infections with candida, *klebsiella*, *nocardia*, *paracoccidioidomyces*, *histoplasma and leishmania*, which are microorganisms with pathogenesis similar to that of mycobacteria [2, 12–13]. In contrast to *Salmonella* infections, *mycobacteria* infections do not reoccur. A BCG vaccination study conducted by Fieschi et al., infection was reported in 36 of 63 patients diagnosed with IL-12R1 deficiency after the vaccination, but no mycobacterial infection was observed in any of these patients. However, *mycobacterial* infections were later reported in 12 of the 27 patients who had not developed an infection immediately after BCG vaccination [14]. BCG vaccine or previous disease has been shown to protect against mildly-virulent *mycobacterial* infections [2,3]. As per the last follow-up, our patient, who was 18 months old at the time of writing, did not develop any *mycobacterial* infections. With early diagnosis and treatment, patients with IL-12R1 deficiency have good clinical prognosis. Diagnosis of IL-12R1 deficiency, the most common genetic defect in MSMD can be made by determination of IL-12R1 expression on the peripheral blood lymphocyte surface (less than 1%) by flow cytometry after in-vitro stimulation with phytohemagglutinin. However, it is critical to perform mutation analysis in order to both identify the disease and provide genetic counseling to the family [15]. In our patient, whose mother and father were third-degree relatives, homozygous NM 005535.3: c.1791 + 2T> G: p. Ala573Leufs * 22 mutations in the IL-12RB1 gene were discovered as a result of whole-exome sequencing analysis. Many studies have found that this essential splice site mutation is pathogenic, causing genetic susceptibility *to mycobacteria*, *salmonella and klebsiella* infections [2]. New mutations and clinical diversity of the disease make genetic investigations crucial in societies where consanguineous marriage is common, as is the case in our country [16].

Patients with local or widespread mycobacterial infections that have developed after BCG vaccination should be evaluated for immune deficiency. As awareness of the clinical features of IL-12R1 deficiency increases, these patients will be diagnosed earlier and easier, especially in countries where consanguineous marriage is prevalent and BCG vaccine is routinely administered.

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