IDCases 23 (2021) e01038

Contents lists available at ScienceDirect

IDCases

journal homepage: www.elsevier.com/locate/idcr

Case report

BCGitis as the primary manifestation of chronic granulomatous disease

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ARTICLE INFO

Article history:
Received 22 November 2020
Received in revised form 21 December 2020
Accepted 27 December 2020

Keywords:
BCG vaccination
BCGiosis
BCGitis
Chronic granulomatous disease
Lymphadenopathy
Primary immunodeficiency disease

ABSTRACT

Patients with primary immunodeficiency disease (PID) are not only vulnerable to mycobacterial disease, but are also more likely to develop adverse events following BCG vaccination. These events can range from regional disease (BCGitis) to disseminated disease (BCGosis). Chronic granulomatous disease (CGD), which is characterized by impaired leukocyte phagocytic function, is one of the many inherited PIDs that increase the body's susceptibility to recurrent bacterial and fungal infections. Here, we report a 6-year-old boy with no significant past medical history who presented with progressive lymphadenopathy six years after BCG vaccination. He was later diagnosed with CGD on further evaluation.

Introduction

Chronic granulomatous disease (CGD) is an inherited defect of leukocyte phagocytic function that increases the body's susceptibility to recurrent bacterial and fungal infections. It is mostly inherited in an x-linked manner; however, autosomal recessive (AR) traits involving both sexes have also been described [1]. Despite the well-known genetic basis of CGD, the exact clinical course and outcome of this disease remains unclear. The clinical manifestation of CGD varies extensively among patients; skin involvement is usually the presenting manifestation but recurrent pulmonary and bone infections, splenomegaly and lymphadenitis may also occur [2–4]. The most frequently cultured microorganisms from infections include *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella, and Aspergillus spp*. [5,6]. Although less frequent, CGD patients are also prone to mycobacterial infections and might experience adverse complications following Bacillus Calmette-Guerin (BCG) vaccination [7].

BCG vaccine, which is a live attenuated vaccine acting against tuberculosis (TB), has existed for more than 90 years. It is administered to all neonates and infants as part of the national childhood immunization program in countries where TB is endemic [8]. For almost all children, BCG vaccination is considered to be safe without any serious complications. Nevertheless, rare side effects ranging from local/regional disease (BCGitis) to distant/disseminated infection (BCGosis) have occasionally been reported [9]. Since BCG is a live attenuated vaccine, the rate of such adverse events is significantly higher among immunocompromised individuals [10].

In this case report, we describe a 6-year-old boy with no significant past medical history who presented with progressive lymphadenopathy six years after BCG vaccination. He was later diagnosed with CGD on further evaluation.

Case report

A 6-year-old boy, born to non-consanguineous parents, was referred to our medical center after presenting with progressive

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http://dx.doi.org/10.1016/j.idcr.2020.e01038

enlargement of axillary and cervical lymph nodes over the last few months. His parents recalled that the lymphadenopathy had initially appeared after BCG vaccination, which was administered as part of the national vaccination program at birth, but had remained stable in size until few months ago. However, at that time, further evaluation had not been considered as the physicians had reassured the parents that this was a normal reaction to the vaccine. The parents denied any significant past medical illness. According to the parent's claim, the patient had no pulmonary, gastrointestinal, genitourinary or cutaneous symptoms and had attained normal developmental milestones. Also, there was no history of recent weight loss.

On physical examination, he was afebrile without any respiratory signs. Multiple non-tender axillary and cervical lymph nodes were palpated. Axillary lymph nodes were on the same side of which he had received the BCG vaccine. No hepatosplenomegaly was detected and his skin examination was normal. Complete blood count revealed a mild microcytic anemia with normal leukocyte and platelet count. Liver tests were within normal limits (Table 1).

A smear of aspirated material from the lymph nodes showed acid-fast bacilli (AFB), and polymerase chain reaction (PCR) assay with specific primers revealed *Mycobacterium bovis*. These findings were consistent with tuberculoid granulomatous lymphadenitis. Considering the patient's clinical presentation, a diagnosis of BCGitis was confirmed. Since BCG complications are more likely in immunodeficient patients, a series of diagnostic tests were performed to assess the competency of the child's immune system. Serum immunoglobulin assay showed elevated levels of serum IgG, IgA, and IgE but normal IgM level (Table 2). Further evaluation with nitroblue tetrazolium chloride (NBT) test to assess the ability of patient's phagocytic cells in producing reactive oxygen species revealed absent dye reduction (NBT = 0%), suggesting intrinsic neutrophil defect.

To confirm the genetic cause of the disease, targeted next-generation sequencing (NGS) covering all known immunodeficiency disease-causing genes was performed, which revealed a missense mutation in the *CYBB* gene located on the X chromosome. All of these findings confirmed the diagnosis of CGD, and thus standard anti-tuberculosis treatment and prophylactic cotrimoxazole, acyclovir and itraconazole were initiated. The patient also received interferon-gamma during hospitalization. Following treatment, the lymphadenopathy began to regress and the patient was discharged in good clinical condition to be followed in an outpatient clinic.

Discussion

Congenital defects of phagocyte number or function are the third most common primary immunodeficiency disorders in Iran, comprising about 17.4 % of all primary immunodeficiencies [11].

Table 1
Initial laboratory investigations.

Lab test	Value	Reference value
Total leukocyte count (mm^3)	5370	4400–12000
Differential cell count (%)		
Neutrophil	62	55–70
Lymphocyte	27	20–40
Monocyte	9.7	2–10
Eosinophil	0.9	0–3
Hemoglobin (mg/dL)	11.4	11.8–14.3
MCV	65.9	77.2–88.5
Platelet count (/μL)	257000	187000–445000
SGOT (U/L)	44	10–45
SGPT (U/L)	22	5–25
Alkaline phosphatase (U/L)	405	179–417

Table 2
Immunologic tests.

Test	Value	Reference range
Serum IgM (mg/dl)	119	37–224
Serum IgG (mg/dl)	1757	386–1470
Serum IgA (mg/dl)	454	25–154
Serum IgE (IU/ml)	240	<135
NBT (%)	0	–

CGD is a heterogeneous genetic disorder in which phagocytes are incapable of killing microorganisms due to a defect in the production of reactive oxygen species [12]. Inactivating mutations in the CYBB gene lead to the most common form of CGD, x-linked (XL) CGD, whereas mutations in the CYBA, NCF1, NCF2 and *NCF4* genes that encode subunits of NADPH oxidase result in autosomal recessive (AR) forms [1,13,14]. In our case, gene sequencing revealed a previously reported but very rare homozygous missense mutation located within the *CYBB* gene on chromosome X: 37668821 leading to an amino acid change; c.1463C > A (p.Ala488Asp) [15]. This mutation has a high damaging prediction score with a CADD score of 32 [16].

In the era of multidrug-resistant TB and the emergence of TB due to the HIV/AIDS epidemic, BCG vaccination has raised more concern, particularly in highly endemic regions for TB. As part of the World Health Organization (WHO) Expanded Program on Immunization (EPI), BCG vaccine is currently administered to all neonates at birth in Iran [8]. Worldwide, with more than 100 million newborns being vaccinated each year, BCG vaccine is believed to be safe for a competent immune system; however, less than one in a thousand vaccinated people develop significant local reactions, and serious disseminated disease develops in fewer than one in a million [17,18]. Previously reported data have shown that 50–76 % of BCG-infected patients suffer from immunodeficiency [7,19]. CGD, severe combined immunodeficiency disease (SCID), Mendelian susceptibility to mycobacterial disease (MSMD) and hyper-IgM syndrome are the most common PIDs associated with adverse events following vaccination [5]. Patients with CGD are more likely to exhibit regional lymphadenopathy after BCG vaccination (BCGitis), while disseminated disease (BCGosis) is less frequent [7]. In its natural course, BCG lymphadenitis can either undergo spontaneous regression or enlarge progressively and become suppurative. The non-suppurative form usually resolves spontaneously within a few weeks without any remarkable sequelae [20]. The timeframe for developing BCG lymphadenitis ranges from two weeks to six months post-vaccination and almost all cases occur within 24 months [21]. Previous studies have shown that in more than 95 % of cases, ipsilateral axillary nodes are enlarged; however, as in our case, supraclavicular or cervical glands may also be involved in isolation or in association with axillary lymph nodes in a minority of patients [21–24]. Furthermore, in the majority of cases, there are only one or two enlarged nodes but as reported in this case, some patients might experience involvement of multiple glands [22]. Another unique feature of the case reported here was the mild course of CGD that delayed its diagnosis. The diagnosis of X-linked CGD is usually established within the first year of life and almost all cases are diagnosed before 5 years of age; however, the mean age at diagnosis is higher in patients with the AR form (8.8 years). In addition, the majority of patients with X-linked CGD experience a severe disease course including severe septicemia and recurrent infections, while patients with AR-CGD manifest a milder phenotype [6]. Despite being diagnosed with X-linked CGD, our patient's presentation was more similar to the AR form. In a study in 2010, Kuhns et al. investigated whether residual reactive oxygen intermediate (ROI) production was associated with survival and disease severity in

patients with CGD. They found that patients with missense mutations in the *CYBB* gene had a higher residual production of ROI compared with patients with nonsense, frameshift, splice or delete mutations within the same gene, while residual ROI production was not significantly different between patients with missense mutations affecting the *CYBB* gene and those with mutations in the *CYBA*, *NCF1*, and *NCF2* genes. More importantly, they showed that patients with higher residual ROI production were significantly less likely to develop severe disease and experienced longer survival times [25]. This finding could possibly explain the relatively milder disease in our patient, as he was diagnosed with a missense mutation in the *CYBB* gene.

BCG vaccination is contraindicated in infants with CGD; however, since the vaccine is administered immediately after birth, many patients are diagnosed with CGD only after BCG complications occur [26]. Thus, in patients with a positive family history, screening for underlying immunodeficiency and postponing vaccination are crucial to prevent adverse events, in particular life-threatening disseminated BCGosis. Since both host (e.g., type of immunodeficiency, age at vaccination) and vaccine-associated factors (e.g., BCG substrain, dose of vaccine) influence the outcome of BCG vaccination, the advent of safer anti-TB vaccines could be an alternative approach in immunodeficient patients [27,28]. Currently, new TB vaccines are being developed following two basic approaches; the first approach is to replace the current BCG vaccine by either improved recombinant BCG or by a genetically attenuated MTB that is safer, more immunogenic and induces protection against highly virulent clinical isolates. Another major avenue to safer TB vaccines is the development of subunit vaccines, which means non-live or non-replicating vaccines can be safely delivered into the human host regardless of immunocompetence [29–31]. Thus, there is hope that in the near future advancement of innovative TB vaccines could help prevent BCG complications in immunodeficient patients.

Source of funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical approval

This study was approved by the ethics committee of Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran.

Consent

Written informed consent was obtained from the patient's guardian for publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Authors' contributions

Nastaran Khalili: Writing-original draft, study design.
Iraj Mohammadzadeh: Data Collection, study design.
Neda Khalili: Writing-reviewing and editing, literature search.
Raúl Jimenez Heredia: Data collection, writing-reviewing and editing.
Samaneh Zoghi: Study design, writing-reviewing and editing.
Kaan Boztug: Data collection, writing-reviewing and editing.
Nima Rezaei: Supervision, project administration, writing-reviewing and editing.
All authors have read and approved the final manuscript.

Declaration of Competing Interest

The authors report no declarations of interest.

Acknowledgments

We wish to thank the patient and his parents for their permission to publish this case report.

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