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BCG-osis after BCG vaccination in immunocompromised children: Case series and review

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ABSTRACT

Bacillus Calmette Guerin (BCG) developed by Albert Calmette and Camille Guerin in France between 1908 and 1921 contained a live attenuated strain of Mycobacterium bovis and was administered worldwide to prevent tuberculosis. BCG vaccination is also administered at birth to all the newborns in Iran. Disseminated BCG infection after BCG vaccination is rare. Here in, we report 2 new cases of disseminated BCG infection and review 15 additional cases identified from our previous retrospective study during a 5-year period from 2005-2010. All of these reported patients were vaccinated. Impaired immunity was detected in 10 cases (59%) including severe combined immunodeficiency, chronic granulomatous disease, Mendelian susceptibility to mycobacterial disease, combined variable immunodeficiency, and HIV infection. Response to therapy was poor among those patients with immune deficiencies, but the overall mortality rate was 32.3%. Disseminated BCG infection is a rare but devastating complication of vaccination. Immune-compromised children are at high risk of developing BCG related complications including regional BCG-itis or disseminated disease; BCG-osis.

Introduction

Bacillus Calmette Guérin (BCG) is an attenuated strain of Mycobacterium bovis that is currently used as a live vaccine for prevention of severe and life-threatening tuberculosis around the world.[1] Although BCG vaccine is considered to be safe, it may cause some complications including: cellulitis and abscesses at the site of inoculation and regional lymphadenitis and disseminated BCG infection or BCG-osis.[2]

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Figure 1: Swollen on proximal joint of left hand index finger

Disseminated BCG infection (BCG-osis) is a rare but most serious complication of vaccination in vaccinized especially immunocompromised children.[1] In this paper, we report the 2 new cases of disseminated BCG infection in addition to the review of 15 cases identified from our previous retrospective study during a 5-year period from 2005-2010.[3]

Case 1

A 2-year old boy was admitted to the infectious disease ward of Hospital in Sari, Iran with chief complaints of fever and swelling on his index finger of left hand and forearm (Fig.1).

A few days before admission, the child had swollen on inferior part of right forearm. Roentgenogram at the time of admission revealed osteomyelitis on the left humerus (Fig.2). His medical history revealed that he was a full term cesarean section delivery and the first child of healthy non- consanguineous parents with gestational age of 37 weeks and birth weight of 3200 gr. He had no history of medicine consumption. A positive family history of TB was found in his father's grandfather.

Figure 2: Osteomyelitis on the left humerus

Figure 3: An ulcer measuring 1×1 cm below the BCG scar on left arm of the patient, mild discharge and erythema with induration of 5.2×5.2 cm around the scar

He has had frequent admissions since birth because of cellulitis and abscesses at the site of BCG inoculation and regional lymphadenitis. He was vaccinated with BCG at birth.

At 10 days of age, he had been admitted because of fever and possible neonatal sepsis and was treated for 10 days. At the age of 7 months, a movable, nontender left axillary lymph node measuring 2×2 cm was developed and gradually became more enlarged. At the age of 9 months, the enlarged lymph node at the left axillary site was drained spontaneously via sinus tract. At the age of 20 months, the patient presented an inflammation on the left upper arm under the BCG inoculation site that gradually became expanded, erythematous and ulceration was developed.

At the age of 22 months, he developed swelling at the proximal joint of index finger of left hand. At hospitalization, on physical examination, he had loss of appetite. The patient had a temperature of 36.7°C and pulse rate: 110, respiratory rate: 20, length: 85 cm, head circumference: 47 cm, weight: 12 kg. There were no abnormal findings in the physical examination of skull, EENT, Neck, chest and heart and no organomegally was observed in abdominal sonography. All of physical finding was limited to:

a) At the site of BCG inoculation, at midpoint of left humerus a cellulitis and ulcerative lesion measuring 1×1 cm below the BCG scar on his left arm. Mild discharge and erythema with induration of 5.2×5.2 cm without tenderness and hotness was observed around the BCG scar and sinus tract at left axillary site (Fig.3).

b) First proximal phalanx was swollen in midpoint with a movable, sausage-shaped nontender mass

c) Laboratory test at the time of admission revealed: WBC= 19200/mm3: (N= 30%, E=5%, M=4%, L=61%), RBC=4.85/mm3, Hb=10.9gr/dl, PLT=499,000/mm3, CRP=2+, ESR=25, and normal U/A. Other laboratory tests were within normal limit. CXR was normal.

Biopsy specimens from vaccination sites demonstrated ulcerated granulomas skin lesion consistent with BCG-itis. A precise diagnosis of BCG-osis was made and quadruple therapy with Isoniazid, Rifampin, Etambutol, Streptomycin and IFN-γ at a dose of $50\mu g/m^2$ was started. The patient recovered thoroughly and was discharged after.

Case 2

A 23-month old girl was admitted to the hospital with fever and abdominal distention. Abdominal sonography and CT scan confirmed mild enlargement of liver. In medical history, it revealed that the patient was healthy and with non-consanguineous parents. She was vaccinated with BCG at birth. She developed axillary lymphadenitis near the BCG inoculation site at the age of 2 months. She had weight loss and disseminated skin Rash (Fig. 4).

Figure 4: Disseminated skin rash on trunk

At the time of admission, besides ESR=80 and WBC= 15000, Neut: 30%, Lymph: 70%, slight elevation of SGOT and SGPT, other laboratory studies were normal. Primary immunodeficiencies investigation showed normal range. Salmonellosis due to Mendelian susceptibility to mycobacterial disease (MSMD) was the precise diagnosis following liver aspiration. The patient was treated with third

generation cephalosporin and IFN-γ therapy and complete recovered after 2 years.

Materials and Methods

In this study, we reviewed 17 cases of Disseminated BCG infection including 2 new cases of disseminated BCG disease, in addition to our 15 patients with disseminated BCG disease, during a 5-year period from 2005-2010. Furthermore, to compare our results in other parts of the world, we conducted a literature review about the Disseminated BCG infection after BCG vaccination in immune-compromised children on Medline in PubMed area, and Google scholar in October 2013 for publications written in English with the following keywords: Bacillus Calmette–Guerin, BCG vaccination, BCG-osis, Mendelian susceptibility to mycobacterial disease, MSMD, Disseminated BCG infection, Complication, IL-12/IL-23, INF-γ, receptor deficiency and children. The evaluation was done first on the title and abstracts for the selection of studies and the full text articles conducted on children were included. Publications were excluded if the studied population was adults or cases resulting from any mechanism other than BCG vaccination.

Results

Our two new cases were classified as definite disseminated BCG disease or BCG-osis based on the evidence of infection at extra regional sites (liver abscesses, axillary lymphadenitis) and a systemic syndrome associated with mycobacterial disease including lymphadenopathy (LAP), osteomyelitis and hepatosplenomegally, fever and weight loss. Table 1 shows the summary of data derived from 15 cases of our retrospective study in addition to the two new cases.

From the 17 patients with BCG-osis, 4 were females. Consanguinity was found in none of our cases. The age range of the patients was between 3.5 to 72 months. Six children (36.3%) were younger than 6-months old and 13 patients (76%) were younger than 12-months old. All of these 17 cases had positive history of the inoculation of BCG vaccine and two or more signs and symptoms of a systemic syndrome compatible with mycobacterial disease including: fever, weight loss, lymphadenopathy or cutaneous abscesses, pneumonia, osteomyelitis and hepatosplenomegaly (HSM). The interval between the administration of the vaccine and onset of the adverse reactions was within 4 months for four cases, between 4 and 12 months in ten cases (59%), and between 12 months and 72 months in three cases. The evidence of BCG infection including a histopathological demonstration of acid-fast bacilli at two or more anatomic sites far from the region of vaccination such as lymph nodes or cutaneous abscesses outside the region of inoculation, liver biopsy, gastric aspiration and bone marrow aspiration were presented in all of the cases. Ten (59%) of the 17 patients had well known primary immune deficiency disorders including severe combined immunodeficiency, chronic granulomatous disease, Mendelian susceptibility to mycobacterial disease, Combined variable immunodeficiency (CVID), and HIV infection. The most common symptoms of BCG-osis were fever (82.4%), lymphadenopathy (82.4%) and hepatosplenomegally (76.5%) presented in all cases. Four patients were developed skin rash and osteomyelitis presented in 3 cases. Five cases were developed pancytopenia and 13 of the patients had weight loss. Impaired immunity was detected in ten cases (58.8%) including five (33.3%) patients with severe combined

Table1. Summary of data on 17 cases of disseminated BCG infection identified at infectious disease ward of the Hospital

No. of case	Sex/Age(Month)	HSM/LAP	Osteomyelitis/ Skin lesion	Fever/ Weight loss	ESR	Anti-Tuberculosis/Immunodeficiency	Outcome
١	F/3.5	+/+	-/-	+/+	٢٠	[a]INH, [b]RMP,[c]SM,[d]IFN/[e]SCID	Died
٢	M/3.5	-/-	-/+	+/+	١٠٢	INH, RMP,SM,IFN/[g]SCID	Recovered
٣	M/6	+/-	-/-	-/+	٧	INH, RMP,SM,IFN/ Unknown	Recovered
٤	M/72	+/+	-/-	+/-	١٣٠	INH, RMP,SM,IFN/ Unknown	Recovered
٥	M/6.5	+/+	-/-	+/+	٩٣	INH, RMP,SM,IFN/ Unknown	Recovered
٦	M/48	+/+	-/-	-/-	٢٥	INH, RMP,SM,IFN/ Unknown	Recovered
٧	F/18	+/+	-/-	+/+	٣٠	INH, RMP,SM,IFN/ Unknown	Recovered
٨	M/10	+/+	-/-	-/-	٣٠	INH, RMP,SM,IFN/SCID	Recovered
٩	M/4	+/+	-/-	-/+	٦٣	INH, RMP,SM,IFN/ Unknown	Died
١٠	M/5	+/+	-/+	+/+	١٣٠	INH, RMP,SM,IFN/SCID	Recovered
١١	M/8	-/+	-/-	+/+	٧٨	INH, RMP,SM,IFN/[h]CGD	Recovered
١٢	F/6	+/+	-/+	+/+	٦٠	INH, RMP,SM,IFN/SCID	Died
١٣	M/11	-/+	+/+	+/+	٧٠	INH, RMP,SM,IFN/CGD	Recovered
١٤	M/5	+/-	+/-	+/+	١٠٠	INH, RMP,SM,IFN/SCID	Died
١٥	M/5	+/+	-/+	+/+	١٣	INH, RMP,SM,IFN/HIV+	Died
١٦	M/24	-/+	+/+	+/-	٢٥	INH, RMP,SM,IFN/ Unknown	Recovered
١٧	F/8	+/+	-/+	+/+	Slight ↑	INH, RMP,SM,IFN/[f]MSMD	Recovered

a(INH):Isoniazid; b(RMP): Rifampin; c(EMB): Ethambutol; d(SM): Streptomycin; e(IFN): Interferon; f(MSMD): Mendelian susceptibility to mycobacterial disease; g(SCID): severe combined immunodeficiency; h(CGD): chronic granulomatous disease

Table 2. Summary of data of the 17 patients with BCG-osis after BCG vaccination derived from selected studies

Author/ Country/Date	No. of case	Sex /Age (M)	HSM/ LAP	Osteomyelitis/ Skin lesion	Fever/ Weight loss	Site(s) of dissemination	Anti-Tuberculosis/ Immunodeficiency/Genetic form	Outcome
[a]Fraitag S/ France/2012	1	M/9	+/?	-/+	+/?	Bone (three patients), lung (two patients), bone marrow (three patients), liver (two patients), spleen (two patients) and gastrointestinal (two patients)	INH,RMP,EMB,SM, IFN-γ/ [d]SCID/ [e]RAG1	Died
	2	M/6	+/?	+/+	+/?		INH,RMP,EMB,SM, IFN-γ, [f]HSCT/ SCID/ IL2Rγ	Alive
	3	M/6	+/?	+/+	+/?		INH,RMP,EMB,SM, IFN-γ, HSCT/ SCID/ IL2Rγ	Alive
	4	M/5	+/?	+/+	+/?		INH,RMP,EMB,SM, IFN-γ, HSCT/ SCID/ IL2Rγ	Alive
[a]Kobayashi M/ Japan/2012	5	M/72	?/+	+/+	-/?	Bone, Skin	INH,RMP,EMB,SM, IFN-γ,/ [g]MSMD/ STAT1 deficiency	Alive
	6	F/5	?/+	+/+	-/?	skin , Bone	INH,RMP,EMB,SM, IFN-γ/ MSMD/ STAT1 deficiency	Alive
[a]Karaca NE/ Turkey/2012	7	M/8	+/+	-/+	+/-	Skin, [a]DLMP, Lung, liver, spleen, abdomen, Cervical [b]LMP	Fludarabine, Busulfan and Anti-timosit globulin, cyclosporine A, HSCT/ MSMD/ CR IFNγR1 deficiency	Died
[a]Hirata O/ Japan/ 2013	8	M/60	?/?	+/+	+/?	Bone, Skin,	Refampicin, Sulfamethoxazole, Trimethoprim, Clarithromycin/ MSMD/ STAT1 deficiency	Alive
[a]Galal N/ Egypt/ 2012	9	F/6	-/+	-/+	+/?	Skin, Bone, Lung, Kideny, [c]GLN	Isoniazide, Rifampicin, Streptomycin, IFN-γ/ Unknown	Alive
	10	M/48	-/+	+/+	+/?		Isoniazide, Rifampicin, Streptomycin, IFN-γ/ Unknown	Alive
	11	F/192	+/+	+/-	+/?		Isoniazide, Rifampicin, Streptomycin, IFN-γ/ MSMD/ IFNγR1 deficiency	Died
	12	M/18	-/+	+/+	+/?		Isoniazide, Rifampicin, Streptomycin, IFN-γ/ Unknown	Died
	13	M/24	-/+	-/-	+/-		Isoniazide, Rifampicin, Pyrazinamide, IFN-γ/ Unknown	Alive
	14	F/18	-/+	-/+	+/?		Isoniazide, Rifampicin, Streptomycin, IFN-γ/ Unknown	Died
	15	M/12	-/+	-/+	+/-		Isoniazide, Rifampicin, Streptomycin, IFN-γ/ Unknown	Alive
	16	F/60	-/+	-/+	+/-		Isoniazide, Rifampicin, Streptomycin, Ethambutol/ Dalacin, IFN-γ/ Unknown	Alive
[a]Kilic SS/ Turkey/2012	17	M/5	-/+	+/+	+/-	Skin, Bone, Lung, GLN, CNS,	INH,RMP,EMB,SM, IFN-γ/MSMD/ IFNγR1 deficiency	Died

a(DLMP): distal lymphadenopathy; b(LMP): lymphadenopathy; c(GLN): general lymphadenopathy; d(SCID): severe combined immunodeficiency; e(RAG1): Recombination Activating Genes 1; f(HSCT): Haematopoietic stem cell transplantation; g(MSMD): Mendelian susceptibility to mycobacterial disease

immunodeficiency (SCID), two patients with chronic granulomatous disease (CGD), one patient with CVID, one patient with MSMD and one with HIV infection. From 17 cases, ten (59%) of cases had good response to four anti-mycobacterial therapeutic regimens including; Isoniazid, Rifampin, Ethambutol, Streptomycin and interferon gamma therapy. From 17 cases, 6 (35%) SCID immune-compromised patients died.

In literature review of disseminated BCG infection in other parts of the world from 2012 to 2013, we identified 17 cases with definite disseminated BCG infection or BCG-osis. These data are summarized in Table 2.

In literature review, of total 17 patients with BCG-osis, thirteen patients (76.5%) were males. Consanguinity was found in eleven of the cases (64.7%). The age range of the patients was between 5 to 192 months. Three children (17.6%) were younger than 6-months and 8 patients (47%) younger than 12-months old. All 17 cases had positive history of the inoculation of BCG vaccine. The interval between the administration of the vaccine and onset of the adverse reactions was within 4 month for 8 cases (47%), between 4 and 12 months in seven cases (41.2%), between 12 months and 72 months in one case. Fever (91.1%), skin lesions (88.2%), lymphadenopathy (76.5%), osteomyelitis (58.8%) and hepatosplenomegally (35.3%) were the most common symptoms of BCG-osis, respectively. The evidence of dissemination of BCG infection at two or more anatomic sites far from the region of vaccination such as bone, lung, liver, spleen, gastrointestinal tract, cervical LMP, kidney, and skin presented in all cases. Skin rash developed in six patients. Ten (59%) of 17 patients had well known primary immune deficiency disorders including SCID (4 cases) and MSMD (6 cases) and remaining cases were unknown. Death occurred in six cases and MSMD was the

underlying immune deficient disorders in half of them. IFNγR1 deficiency (3 cases) and STAT1 deficiency (3 cases) were the genetic forms of MSMD identified in these patients.

From 17 cases, eleven (67.7%) cases had good response to four anti-mycobacterial therapeutic regimens including; isoniazid, Rifampin, Ethambutol, streptomycin and interferon gamma therapy. From three patients with SCID underwent Haematopoietic stem cell transplantation (HSCT) from a related haplo-identical donor, one died at day 74 post-HSCT from graft vs. host disease (GVHD) and one patient with MSMD underwent HSCT from the match unrelated donor died after a septic attack.

Discussion

BCG vaccination has been in use since 1921 and employed to immunize newborns routinely in most regions of the world. Annually, one hundred twenty (120) million doses of BCG vaccine are administered worldwide.[10, 11] BCG vaccination is administered to all newborn at birth in Iran. Although different studies have shown that the complications of BCG vaccination appear within 6 months of birth,[12] the results of our study showed 76% of our cases were younger than 12 months. Similar to the study of Khalilzadeh et al., we showed the incidence of disseminated BCG infection is more common in boys as compared to girls.[13] This result has been confirmed by our recent literature review. Consanguinity was found in eleven (64.7%) of our patients in literature review compared to non consanguinity among our reported cases.

Although, BCG vaccines are considered extremely safe in immune-competent hosts, complications do occur.[14] Lymphadenitis, fistula formation and rarely disseminated disease and death may occur. Disseminated BCG infection is the most serious complication of BCG vaccine that may occur in children with

immunodeficiency disorders.[15] In rare occasion, BCG vaccination results in disseminated infection involving lymph nodes, lungs, kidney, spleen and other organs. These disseminated infections are referred to as "BCG-osis" as complications of BCG injection, with high mortality rates (71%).[9] In our reported cases, BCG-osis were demonstrated with fever (82.4%), lymphadenopathy (82.4%), hepatosplenomegally (76.5%), skin rash and, osteomyelitis (17.6%). All of these symptoms including fever (91.1%), lymphadenopathy (76.5%), skin lesions (88.2%), and osteomyelitis (58.8%), excluding hepatosplenomegally (35.5%) were presented more sever in our patients in literature review.

BCG-osis is consistently indicated the presence of an underlying impaired immunity, such as SCID, CGD, HIV infection and MSMD.[16] In half of patients with present MSMD, and about half of the known MSMD patients have been shown to present an inherited defect of the IL-12-INF-g axis, whereas the remaining cases remain asymptomatic.[13]

The records of our 17 cases confirm that the most patients with disseminated BCG disease had impaired immunity. Impaired immunity was detected in 10(59%) of the 17 cases including SCID, MSMD, CGD, CVID, and HIV infection. The prevalence of primary immune deficiency disorders was similar in both of our investigations. SCID is the most severe form of Primary immunodeficiency diseases (PIDs) and BCG-osis as a side effect of BCG vaccine could be seen in all underlying genetic types of SCID. SCID is considered as an emergency in pediatric practice that early detection and appropriate treatment can prevent the life- threating complications.[6] SCID was also the most PIDs among our cases and it was also the main cause of death among our 17 recorded cases. Whereas, in our literature review, MSMD was the main PIDs and the main cause of death in half of the cases.

Recessive complete IFNγR1 deficiency (3 cases) and STAT1 deficiency (3 cases) were the genetic forms of MSMD identified in these patients. Recessive complete IFN-γR1 deficiency causes selective susceptibility to early onset and severe mycobacterial infection and is associated with severe, often fatal infection with BCG and environmental mycobacteria (EM) as the leading cause of the disease in all IFN-γR1 deficient patients in early childhood.[15-17] The overwhelming infections involve several organs such as soft tissue, lymph node, bone marrow, skin, lung and manifested by fever, loss of weigh, lymphadenopathy and hepatosplenomegally.[26] The prognosis of patients with IFN-γR1 deficiency is poor and IFN-γ therapy is not effective due to the absence of functional receptors. Haematopoietic stem cell transplantation (HSCT) has been used in a few patients.[20, 27] IFN-γ therapy is ineffective due to the lack of specific receptors and overwhelming mycobacterial infections.[28] All 3 patients with IFNγR1 deficiency in our literature review had two or more than of mentioned above manifestations and had no response to the therapy and all of them died. IL-12RB1 deficiency is the most common type of MSMD among the known genetic disorders predisposing the affected individuals to mycobacterial infections. Severity of the disease varied from asymptomatic cases in adulthood to cases died in early years of life due to side effects of the disease. The mortality rate was mostly secondary to BCG-osis or EM disease.[29-31] In symptomatic patients, infectious diseases occur before the age of 12 months and the clinical prognosis of the patients with IL-12RB1 deficient is quite good especially following molecular diagnosis, preparing careful follow-up and aggressive and prolonged treatment with multiple antibiotics and recombinant IFN-γ. Removing mesenteric and splenic lesions is necessary in cases with poorly

available antibiotics and IFN-γ. There is no indication to HSCT in patients with IL-12RB1 deficiency.[14] IL-12RB1 deficiency was identified in one of our cases who had salmonellosis and treated by third generation of Cephalosporin as an antimicrobial agents and IFN-γ therapy and completely recovered after 2 years. The most common symptoms of BCG-osis in this case were fever, lymphadenopathy and hepatosplenomegally and skin lesions.

Chronic granulomatous disease is a heterogeneous genetic disorder in which the phagocytes are not capable to kill microorganisms. It has been documented that some CGD patients are predisposed to infections with M. tuberculosis increasingly, but it is still a debate. Vaccination with attenuated M. bovis BCG vaccine could result in BCG-osis in these patients practically. Review of literature reveals controversies on complications of BCG in CGD patients. CGD patients are more likely to show BCG lymphadenitis. However, they are more prone to cure with anti-TB regimen in contrast to the SCID patients. BCG vaccination is contraindicated in infants with CGD, but due to countrywide BCG vaccinations at birth, most patients are diagnosed with CGD after being vaccinated and developing BCG complications.[32-37] We found CGD in one of our cases. He had BCG vaccination at birth. Fever, lymphadenopathy, osteomyelitis and weigh loss were the most common findings in this case. Quadruple anti-microbial therapy associated with IFNγ was effective and the patient recovered completely.

There have been several reports about local and disseminated devastating complications developed in HIV patients vaccinated with BCG.[38] HIV has been identified in one of our cases. All of the symptoms of a systemic syndrome were compatible with mycobacterial disease with an expecting of osteomyelitis were

demonstrated in this case. The patient died in spite of administration of anti- TB regimen and IFNγ therapy.

The most cause of death in our cases was SCID immune deficiency with a mortality rate of 35.3%. Whereas, in a study by Casanova et al., the morality rate of BCG infection was reported as 43% higher as compared to our result.[23] The mortality rate reported by Afshar Paiman et al. was 58.8% despite the aggressive management.[2] Determining a genetic diagnosis is important for patients with disseminated mycobacterial disease as well as for prognosis and treatment of the diseases. Although, there is not a defined genetic aetiology in about half of all the patients with MSMD,[16] flow cytometry has proven to be useful in patients with genetic defects associated with Mendelian susceptibility to mycobacterial disease by focusing on the evaluation of specific surface protein expression and cell function analysis.[39] The accurate molecular diagnosis is critical to determine the optimal treatment strategy for each patient. In complete IFN-γR1 deficiency, the manifestation of lepromatous-like lesions following BCG immunization is suggested absent of IFN-γR1 mediated immunity, whereas, tuberculoid granulomas almost definitely rule out complete IFN-γR1deficiency. Regardless of the underlying genetic etiology, appearances of NTM lesions are generally lepromatous-like.[40]

Skin biopsy is a crucial diagnostic tool because a skin rash can be the first sign of immunodeficiency and valuable in evaluating the severity of the underlying immunodeficiency. The microscopic pattern consists of 'lepromatous-like' inflammation or a mycobacterial spindle like tumor (MSP), can indicate that immunodeficiency is more likely to be severe. Gantzer et al. in 2013 revealed that an early skin biopsy after HSCT in patients with recent-onset or worsening skin lesions can be used to differentiate between BCGitis and

Immune reconstitution inflammatory syndrome (IRIS) related lesions. Moreover, skin biopsies are essential diagnostic tool for pediatricians, allowing them to monitor both the course of BCGitis after HSCT and the quality of immune restoration. A shift from 'lepromatous' features to 'tuberculoid' features was correlated with a good prognosis, while granuloma was absent, even after the administration of anti-mycobacterial treatment and INF-γ therapy.[41]

Of the 17 recorded cases, 4 (23.5%) patients had skin rash, whereas, we identified skin lesions in 15 (88.2%) of patients in the literature review.

There is pessimism in the historic literature review about the treatment of disseminated BCG infection in immune-compromised patients.[2] The treatment of disseminated BCG infection is consisted of anti-bacterial, anti-tuberculosis in addition to INF-γ in selected cases.[42] More advanced treatment procedures, such as HSCT or gene therapy are also used to improve the prognosis of such patients.

From 17 of the recorded cases, eleven (67.7%) cases had good response to four anti-mycobacterial therapeutic regimens including; isoniazid, Rifampin, Ethambutol, streptomycin and IFN-γ therapy. None of the patients underwent HSCT. Response to therapy was poor among those patients with immune deficiencies, but the overall mortality rate was 35.3%. IFN-γ therapy was started for 13 (76.5%) of the cases. Response to IFN-γ was good in 59%. Patients with SCID had no response to IFN-γ therapy and the mortality rate was 100%.

Comparing with the 17 recorded cases, in our literature review, the patients showed good response to four anti-mycobacterial therapeutic regimens including; isoniazid, Rifampin, Ethambutol, streptomycin and IFN-γ therapy in 67.7%. Response to HSCT treatment was fairly good (50%). From three patients with SCID who underwent HSCT by a related haplo-identical donor, one died at day 74 post-HSCT from graft vs. host disease and one patient with MSMD underwent HSCT from the match unrelated donor died after a septic attack.

Moreover, the patients with MSMD are prime candidates for adjuvant immunotherapy in the form of exogenous cytokines to overcome the deficits at molecular level.[43] Given the setting of ideal mycobacterial susceptibilities, patient compliance, and drug availability, long term treatment is required and can be extended to years for drug-resistant strains. Unfortunately, many of the NTM are highly drug-resistant that cause simple therapy almost impossible.[44] Bone marrow transplantation is considered as the best treatment in children with complete IFN-γR1 and IFN-γR2 deficiencies. HSCT has been an effective treatment in a few of the patients.[27, 40,45] IFN-γ therapy is not effective in these children due to the absence of functional receptors and mycobacterial infections are overwhelming. Anti-mycobacterial drugs may be sufficient in children with partial IFN-γR deficiency, but IFN-γ therapy may also be of benefit. HSCT is not indicated in recessive partial IFN-γR1 deficient patients. Because of sharing the similar pathogenic mechanism in patients with complete IL-12p40 or IL-12R1, antibiotics and IFN-γ therapy are likely to be effective in these patients.[31,32] Partial IFN-γR2 deficiency affected patients should be treated with IFN-γ. Furthermore, glycosylation inhibitors might be beneficial in patients with complete or partial IFN-γR2 deficiency due to misfolding or gain-of- glycosylation receptors.[46] The prognosis of children with complete IFN-γR deficiency is poor and typically has severe poorly delimited, multibacillary, with no epithelioid or giant cells and may lead to death because of overwhelming infection, whereas the children with tuberculoid granulomas identified by well delimited, paucibacillary, with epithelioid and giant cells have a good outcome.[44] The patients with partial IFN-γR

deficiency due to mutations of either autosomal recessive or autosomal dominant IFN-γ receptor usually have less severe mycobacterial disease associated with tuberculoid granulomas. Although the clinical phenotype in IL-12 p40 deficiency and IL-12Rb1 deficiency is typically milder than that of complete IFN-γR deficiency, the disorders are also associated with raised susceptibility to infections with BCG, NTM, and Salmonella.[24]

Conclusion

Disseminated BCG infection is a rare but devastating complication of BCG vaccination that should be considered in the appropriate clinical setting. Severe immune-compromised infants are at greatest risk and they respond poorly to standard therapies.

To prevent BCG complications, screening should be performed for MSMD, CGD and other PIDs before BCG inoculation in individuals with positive family history of PIDs, precisely the resident in the regions with high rates of consanguinity and delaying BCG vaccination as another option. Taking a good family history in such patients could be beneficial and may lead to an early diagnosis, which in return would result in early intensive treatment and could be life-saving in these patients.

Conflict of Interest

The authors have no conflicts of interest to declare.

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