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Complicated BCG vaccination during chemotherapy in infant acute leukemia patients

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Summary

BCG vaccination complications, such as BCGitis and BCG-osis are relatively rare complications, which may occur in immunocompromised patients, including infants with hematological malignancies receiving chemotherapy. There is currently very few published data complicated BCG vaccination cases in infants with hematological malignancies. We report 2 children with infant acute leukemia developing BCG vaccination complications demonstrating a multidisciplinary therapeutic approach needed in these cases.

Keywords

Acute myeloid leukemia, acute lymphoblastic leukemia, infants, BCG-itis, BCG-osis, allogeneic stem cell transplantation.

Introduction

According to the World Health Organization, the Russian Federation is among 30 countries with high tuberculosis burden. BCG vaccine has a proven protective effect against tuberculous meningitis and disseminated tuberculosis in children [1]. The Bacillus Calmette-Guérin (BCG) vaccine is produced from a live and attenuated strain of Mycobacterium bovis. In Russian Federation the primary BCG vaccination is mandatory for all newborns is at 3-7 days of life. Although vaccination with BCG is considered to be safe, it may cause regional (BCG-itis) and disseminated (BCG-osis) complications in immunocompromised host. As it is given early in life, some patients may receive the vaccine before some specific contraindications are revealed.

There is currently no systematic published data on complicated BCG vaccination in infants with acute leukemia. The term "infant leukemia" generally refers to acute lymphoblastic leukemia (ALL) diagnosed in patients younger than 1 or acute myeloid leukemia (AML) registered in children younger than 2 years [2].

We report 2 cases of children with infant acute leukemia developing BCG vaccination complications and demonstrate a possible therapeutic approach to this condition.

Case descriptions

Clinical case 1

A 1-month-old girl was admitted to R.M. Gorbacheva Children Research Institute in February 2020. She was a term neonate (birth weight 3.130 kg) born by normal vaginal delivery. The mother underwent regular prenatal check-ups revealing vaginal candidiasis and anemia of pregnancy. The patient

received BCG-M vaccine on the 3rd day of life. In February 2020, routine CBC performed in a 9-day-old neonate have shown a high WBC counts of 265×10^9/l with 43% of blast cells in peripheral blood. The diagnosis of infant AML, FAB M4, XX t(2;11) with KMT2A rearrangement was established. At the time of the diagnosis the patient had no clinical signs of any disease. Patient received 1st AM42E chemotherapy course according to AML-MRD 2018 protocol with a dose reduction due to young age and was then referred to R. M. Gorbacheva Children Research Institute for further treatment. Upon admission to the clinic on February 19th 2020, the pancytopenia (Hb 69 g/l, Plt 2×10^9/l, WBC 1.5×10^9/l) and high serum C-reactive protein level (156 mg/l) were found, thus leading to diagnosis of febrile neutropenia. The examination on admission revealed skin hyperemia at the BCG-M vaccination site and elbow area of the arm (Fig. 1). Empirical therapy regimen consisting of meropenem, linezolid, and anidulafungin was administered.

Figure 1. BCG-itis in Patient No.1

The chest X-ray (Fig. 2) and computed tomography (Fig. 3) have been performed in order to find possible sings of generalized BCG infection did not yield any abnormal findings.

According to pediatric phthisiologist's recommendation, isoniazid was administrated in order to control BCGitis symptoms and prevent the spread of BCG infection possible due to AML therapy-associated immunosuppression. Along with systemic therapy the local treatment consisting of dimexide lotion and hypertonic solution were used.

The signs of local BCGitis resolved after one month after treatment initiation.

In April 2020, the patient achieved complete remission with minimal residual disease persistence registered by flow cytometry. The child then received hAM chemotherapy regimen instead of FLAida, which should have been given according AML-MRD 2018 protocol, due to the risk of life-threatening generalized BCG-infection. By the end of May 2020, the patient was found to be COVID-19 infection PCR test-positive without clinical or CT signs of infection. In July 2020 he received 3 anti-Covid-19 convalescent plasma transfusions (10 ml/kg) due to prolonged SARS-CoV-2

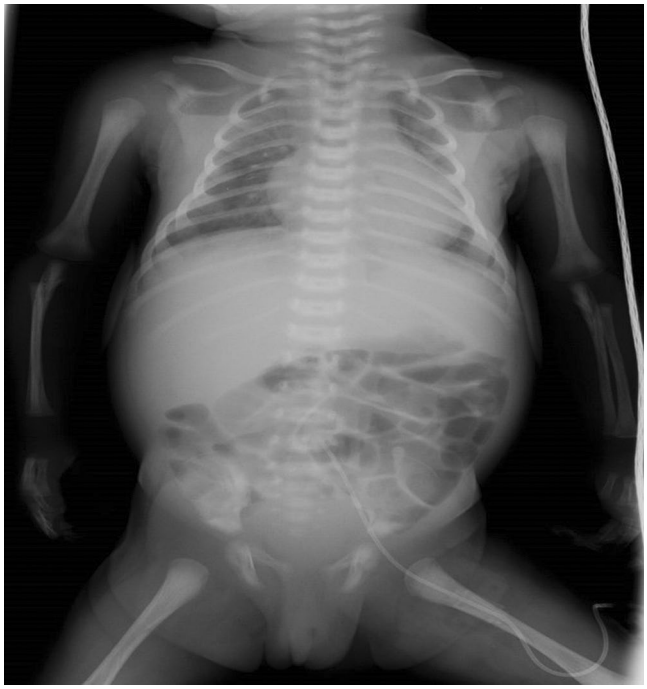

Figure 2. Chest X-ray pattern of Patient No.1

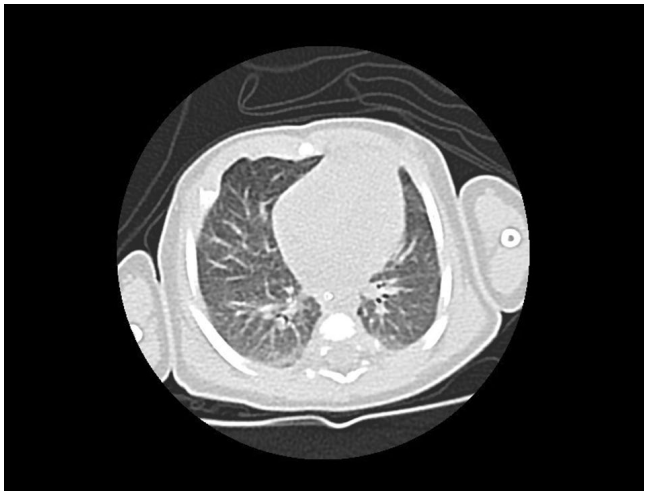

Figure 3. Chest CT scan of Patient No.1

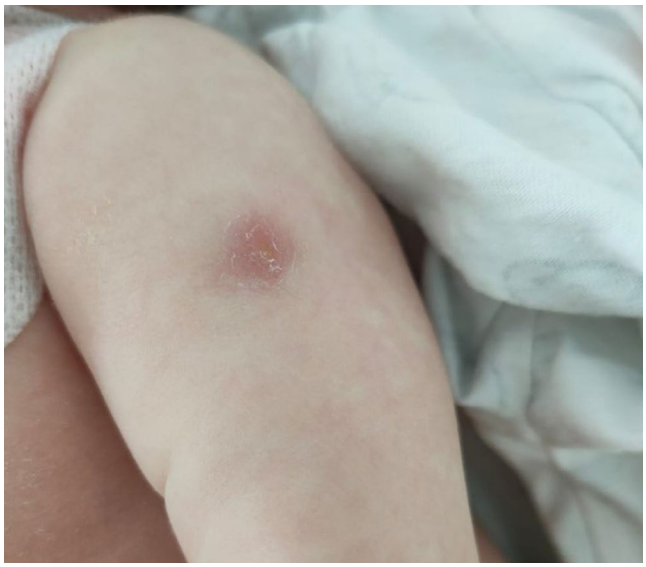

Figure 4. BCG-itis resolution after treatment in Patient No.1

persistence. The SARS-CoV-2 negative status was achieved after the second transfusion. Haploidentical allogeneic stem cell transplantation was performed on 24th of July in complete remission. Conditioning regimen consisted of intraveneous busulfan (12 mg/kg) and fludarabin. Graft-versus-host disease prophylaxis included post-transplant cyclophosphamide, tacrolimus and everolimus. Engraftment was achieved on day +20. By June 2022 the patient has full donor chimerism, there are no signs of AML and no symptoms of BCG infection.

Clinical case 2

A 1-month-old girl was admitted to R.M. Gorbacheva Children Research Institute in August 2019. The child was born from the second pregnancy (second birth) by caesarean section. She received BCG-M vaccine on the 3rd day of life. Then, as the child was one month old, the routine check-up revealed hepatosplenomegaly. The CBC have shown a high WBC count of 112×10^9/l with 90% of blasts. Also 76.2% of lymphoblasts with CD45dim/SSClow/CD19+/CD38+/CD123+/CD10-/CD20-/CD22-/CD7-/CD117-/CD33-/CD13-/CD64-/CD15-/sIgM-/cytIgM-/MPO-/cytCD3-/cytCD79a+ immunophenotype were found in bone marrow, which corresponded to B-I ALL (EGIL). The blasts cytogenetics was characterized by chromosome rearrangements 46,XX,t(11;19)(q23;p13)[4]/46,XX[16]. The girl was enrolled in Interfant 2006 protocol with 2/3 dose reduction during remission induction due to young age at diagnosis. The hematological remission and MRD-negative status by flow cytometry and molecular biology test were achieved on day 36. She then proceeded to consolidation therapy (Protocol IB) starting on 17th of September 2019. On day 5 of consolidation regimen the 9-mm upper left shoulder (BCGm vaccination site) infiltrate with central pustule appeared, although the child had not yet developed post-chemotherapy cytopenia. The regional lymph nodes were not enlarged. According to pediatric phthisiologist's recommendation isoniazid was added to antimicrobial therapy regimen (already containing meropenem, linezolid and anidulofungin). The chemotherapy was suspended till BCGitis regression (de-evolution of pustules and crusts formation). After BCGitis resolved isoniazid treatment stopped due to hematological toxicity (agranulocytosis) development. An allogeneic hemopoietic stem cell transplantat from matched related donor was performed on 12th of November 2019 with conditioning regimen consisting of intravenous busulfan (12 mg/kg) and fludarabin. The graft-versus-host disease prophylaxis was post-transplant cyclophosphamide-based. On day +27 post HSCT the MRD-negative remission with partial (40%) donor chimerism were registered. The patient received donor lymphocyte infusion in order to boost donor chimerism. Then, 1st isolated bone marrow relapse was diagnosed on day +63. The patient received FLAG chemotherapy in January 2020. However in February 2020 ALL progression (75% of CD22-positive blasts in bone marrow) was confirmed. The 3 weekly inotuzumab ozogamicin infusions (0.8 mg/m^2, 0.5 mg/m^2, and 0.5 mg/m^2) were administered leading to MRD-negative remission achievement on 5th of March 2020. Then, on 16th March 2020 the patient received a second allogeneic stem cell transplantation from haploidentical donor (father). Conditioning regimen consisted of treosulfan (36 g/m^2) and fludarabin, the graft-versus-host disease prophylaxis included post-transplant cyclophosphamide and sirolimus. Engraftment was registered on day +17. The patient developed a Grade2 skin acute graft-versus-host disease successfully treated by glucocorticoids administration. By June 2022 she is alive, in remission, and retains full donor chimerism. The growth and development are normal.

Discussion

Adverse reactions to BCG vaccination are likely to be substantially underreported with only 1-10% of them being registered [3, 4]. These complications may be mild as well as severe. For the mild complications, e.g., cutaneous lesions (hyperemia, swelling, soreness, abscess formation, keloid and blister formation), the rate is estimated to be less than 1/1,000. Local ulceration at the vaccination site, suppurative lymphadenitis, osteitis, osteomyelitis, and disseminated BCG infection are severe complications, which occur in approximately two cases *per* 1 million of vaccinations [5].

Although BCG vaccination is contraindicated in patients with cancer, the majority of children are immunized at birth before the diagnosis is established. We describe two different cases of BCG vaccination complications, which may have very different pathogenesis. The first case demonstrates opportunistic BCG infection development in patient with profound cytopenia and immune deficiency. The second BCGitis case developed past CBC counts recovery and may be explained by immune reconstitution inflammatory syndrome. Immune reconstitution syndrome is usually presented in patients with HIV receiving highly active antiretroviral therapy (HAART) and is defined as paradoxical worsening of an opportunistic infection correlating with immune recovery [6]. This phenomenon is not unique to HAART recipients and has also been described in context of high-dose systemic steroids and chemotherapy withdrawal [7, 8].

There are currently no guidelines for anti-mycobacterial therapy and prophylaxis in infants with history of BCG vaccination at birth developing secondary immune deficiency due to hematological malignancy and chemotherapy. Also, different approaches are used to manage immune reconstitution syndrome-associated BCGitis, including surgical debridement, needle aspiration, steroids and anti-mycobacterial treatment. In some cases spontaneous resolution without intervention or antibiotics has occurred [9]. In our patients the BCGitis was successfully treated by chemotherapy suspension and combination of local and systemic antimycobacterial treatment.

Conflict of interests

None declared.

References

1. Global tuberculosis report, WHO 2020. Access: www.who.int/publications/i/item/9789240013131

2. Brown P. Treatment of infant leukemias: challenge and promise. Hematology Am Soc Hematol Educ Program. 2013;2013:596-600. doi: 10.1182/asheducation-2013.1.596

3. Lotte A, Wasz-Hockert O, Poisson N, Engbaek H, Landmann H, Quast U, et al. Second IUATLD study on complications induced by intradermal BCG-vaccination. Bull Int Union Tuberc Lung Dis. 1988; 63(2):47-59. PMID: 3066422

4. Lotte A, Wasz-Höckert O, Poisson N, Dumitrescu N, Verron M, Couvet E. BCG complications. Estimates of the risks among vaccinated subjects and statistical analysis of their main characteristics. Adv Tuberc Res. 1984;21:107-193. PMID: 6475644

5. Tural-Kara T, Ozdemir H, Erat T, Yahsi A, Ciftci E. Local Cutaneous complications after bacille Calmette-Guerin vaccine: Experience of a single center. Int J Clin Pediatr. 2017;6(3-4):37-41. doi: 10.14740/ijcp279w

6. Alexander A, Rode H. Adverse reactions to the Bacillus Calmette-Guerin vaccine in HIV-positive infants. J Pediatr Surg. 2007;42(3):549-552. doi: 10.1016/j.jpedsurg.2006.10.059

7. Barretto J, Wirk B. Early recognition of immune reconstitution inflammatory syndrome leads to avoidance of endotracheal intubation. World J Oncol. 2012;3(4):194-198. doi: 10.4021/wjon527w

8. Miceli MH, Maertens J, Buve K, Grazziutti M, Woods G, Rahman M, Barlogie B, et al. Immune reconstitution inflammatory syndrome in cancer patients with pulmonary aspergillosis recovering from neutropenia: Proof of principle, description, and clinical and research implications. Cancer. 2007;110(1):112-120. doi: 10.1002/cncr.22738

9. Puthanakit T, Oberdorfer P, Punjaisee S, Wannarit P, Sirisanthana T, Sirisanthana V. Immune reconstitution syndrome due to bacillus Calmette-Guérin after initiation of antiretroviral therapy in children with HIV infection. Clin Infect Dis. 2005;41(7):1049-1052. doi: 10.1086/433177

Осложненное течение вакцинации БЦЖ у детей до года с острыми лейкозами на фоне химиотерапии

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Резюме

Осложненное течение вакцинации БЦЖ считается редким состоянием, однако иммунокомпрометированные пациенты, в том числе дети раннего возраста с гемобластозами на фоне химиотерапии, имеют высокий риск развития данного нежелательного явления. На сегодняшний день в литературе отсутствует информация о ведении осложненной вакцинации БЦЖ у пациентов с младенческим лейкозом.

Мы сообщаем о 2 случаях успешного лечения пациентов с младенческим лейкозом, у которых на фоне химиотерапии имелось осложненное течение вакцинации БЦЖ, и демонстрируем наш мультидисциплинарный терапевтический подход.

Ключевые слова

Острый миелоидный лейкоз, острый лимфобластный лейкоз, дети младшего возраста, БЦЖ-вакцинация, осложнения, аллогенная трансплантация гемопоэтических клеток.