

Reactivation at BCG Vaccination Site in a Case of Multisystem Inflammatory Syndrome in Children

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Abstract

Background: Kawasaki disease is a well known entity in pediatric age group and so is its counterpart Multisystem Inflammatory Syndrome in Children (MIS-C). MIS-C term became more popular during covid era as the infection started to affect pediatric age group. Now, a large number pediatricians have seen cases of MIS-C. Reactivation of BCG scar is less commonly seen in Kawasaki disease and rare to never in a case of MIS-C.

Case Presentation: We report a 6-month-old male child who presented with cold and fever. Covid Rapid Antigen Test (RAT) and Covid RTPCR were negative. He continued to have high grade fever which is unusual for a case of bronchiolitis and started on antibiotics. Clinical suspicion of MIS-C made and started to work up for the same. Examination revealed reactivation at BCG site with peeling of skin. Further investigations showed elevated CRP and d-dimer with positive anti-SARS COV2 antibody. Diagnosis of MIS-C confirmed and treated with methylprednisolone and IVIG.

Conclusion: Reactivation at BCG site is well known entity in Kawasaki disease and as a post vaccination immune cross reactivity. But never reported in a case of MIS-C as less known about human immunological response towards Covid-19 infection and its sequel. It can be considered as an early diagnostic tool in resource poor settings and at community level.

Keywords: Multisystem Inflammatory Syndrome in Children; BCG scar; IVIG; Methylprednisolone.

INTRODUCTION

Pandemic of Covid 19 had created chaos all over the world. It did not spare any age group

from its devastating effects. It was more deadly initially in high-risk groups and old ages with little or no effects among children. At first it was a new infection and its behaviour, early and late effects were not known. As time passed, we could be able to appreciate spectrum of manifestation of the Covid infection. Protocols were made to curtail the infection and so for its early detection and management. Research on drugs that are effective in treating Corona infection started and various drugs were proposed to be effective. However, only a countable number of drugs showed benefits. Covid-19 even had varied effects on the foetus of

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Covid infected mother such as intrauterine death, hydrops fetalis, congenital covid infection and so on. As children started infecting with Corona virus, we could see a variety of presentation from asymptomatic to devastating complication of the infection so called Multisystem Inflammatory Syndrome in Children (MIS-C).¹ Reactivation of the BCG scar has been described in children during viral infections and following influenza vaccination, but is mostly associated with Kawasaki's disease, a disease entity with pathogenesis likely similar to the Covid-19 complication, MIS-C.² We present a case of MIS-C with reactivation at BCG site.

CASE PRESENTATION

A 6-month-old male child presented with history of cold and fever of 3 days duration. Child was admitted in view of tachypnoea and decreased air entry over left mammary region. Chest X-ray was suggestive of bilateral diffuse haziness with hyperinflation suggesting bronchiolitis as in fig.



Fig. 1: Chest X-ray suggestive of Bronchiolitis.



Fig. 3: Healing at BCG reactivation site 1 week after IVIG treatment.

1 and hence initial diagnosis of bronchiolitis was made and started on humidified oxygen. Complete hemogram was done suggestive of anemia (Hb-9.2g/dl) with elevated total leukocyte count and normal platelet count (Table 1). Child continued to have fever spikes of 101 to 103. Dengue serology (NS1 antigen, IgM and IgG), Rapid malarial antigen test, peripheral smear for malaria parasite, Covid RAT and Covid RTPCR were negative. All possible causes of acute febrile illness were ruled out and started on inj. Amoxicillin and clavulanic acid. Blood culture and Urine culture were sterile without any bacterial growth. Child continued to have persistent fever and had 2 episodes of vomiting. Child developed erythema at BCG site with peeling of skin. Child had 2 system involvement with fever for 5 days and elevated CRP and D-dimer levels (Table 1). Hence, Possibility of MIS-C considered and level for anti-SARS COV2 antibody sent.³ 2D Echocardiogram was done which was suggestive of small ASD with normal coronary vessels. ECG was normal with negative Trop I level. Child was



Fig. 2: BCG site reactivation.

started on inj. Methylprednisolone (2mg/kg/day) in view of strong evidences in favour of MIS-C (reactivation at BCG site along with other criteria) along with inj. Low molecular weight (LMWH) (2mg/kg/day) and aspirin (5mg/kg/day). Child started responding and temperature returned to baseline. On receiving Anti-SARS COV2 antibody levels (29.6U/ml), diagnosis of MIS-C confirmed.³ Patient was started on IVIG 2g/kg. Inj. Methylprednisolone was changed to equivalent dose of oral prednisolone and tapered slowly over

5 days and repeat D-dimer was 435 ng/ml at the time of discharge. Patient was advised to follow up for 2D echocardiogram.

DISCUSSION

Infections with SARS-CoV-2 in pediatric age

Table 1: Investigations with normal reference range.

Parameter	Observed value	Reference value
Hemoglobin	9.2 g/dl	11.1-14.1 g/dl
Leukocyte count	15620 cells/cumm	6000 – 18000 cells/cumm
Platelet count	3.58×10 ⁵ /cumm	2-5.5×10 ⁵ /cumm
CRP	42.8 md/l	0-10 mg/dl
ESR	56 mm/ at 1hour	2-15 mm/ at 1 hour
PT	12 seconds	11-16 seconds
aPTT	26 seconds	26-36 seconds
INR	0.8	-
BUN	15 mg/dl	15-50 mg/dl
Creatinine	0.4 mg/dl	0.4-14 mg/dl
Blood culture	Negative	-
Urine culture	Negative	-
D-dimer	1345 ng/ml	Up to 500 ng/ml
Urine Routine and microscopy	Within normal limits	-
Anti-SARS COV-2 antibody	29.6U/ml	< 0.80 U/ml (negative) ≥0.80 U/ml (positive)

group are usually mild, but there may be dreaded complications associated with post infection inflammatory disorder, which can lead to serious short term and long term consequences, referred to here as MIS-C. Most cases of MIS-C associated with COVID-19 are treated following the standard protocols for Kawasaki disease. Dufort et al. highlight that the incidence of MIS-C was 2 per 100,000 in children and young adults of less than 21 years of age.¹ MIS-C is equivalently severe to Kawasaki disease, based on six main diagnostic elements: pediatric age, persistent fever, presence

of laboratory inflammatory markers (ESR, CRP), signs or symptoms of organ dysfunctions, without any alternate diagnosis, and history of COVID-19 infection or exposure with possible cardiac involvement.³ World Health Organization and the Centers for Disease Control and Prevention (CDC), have defined the diagnostic criteria of MIS-C.(Table 2)

The presence of coronary aneurysm is a serious complication, well known in Kawasaki disease, and present in MIC-S. Coronary artery inflammation

Table 2: Multi-system Inflammatory Syndrome in Children (MIS-C): WHO Definition³

0-19-years-old child with fever >3 days
And: Two of the following:
1) Rash or bilateral non-purulent conjunctivitis or muco-cutaneous inflammation signs (oral, hands or feet).
2) Hypotension or shock
3) Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (ECHO findings or elevated Troponin/NT proBNP)
4) Evidence of coagulopathy (by PT, PTT, elevated d-Dimers)
5) Acute gastrointestinal problems (diarrhoea, vomiting, or abdominal pain)
And Elevated ESR, C-reactive protein or Procalcitonin
And no other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes.
And Evidence of COVID-19 (RT-PCR, antigen test or serology positive), or likely contact with patients with COVID-19

will progress to aneurysm which acts as a nidus for thrombus formation with partial or complete artery block resulting in myocardial infarction, and cardiac arrhythmias. The timely diagnosis and treatment with Intravenous Immunoglobulins (IVIG) until the end of first week of the disease reduced the possibilities of these complications.⁴ The child described in this case report had MIC-S without heart involvement as confirmed by ECG, echocardiography and acute cardiac markers and was treated using steroid and IVIG.

In countries like India where tuberculosis is still a major public health issue, BCG is recommended to all neonates at birth or as soon thereafter as possible. In countries with low incidence of TB (European countries) BCG vaccine is only given to high-risk groups. Up to 97% of people who receive BCG vaccine experience a skin reaction at the injection site 2 to 4 weeks after vaccination.^{5,6} The reaction heals within 2 to 5 months with a scar of approximately five mm in diameter. Several research studies concluded that BCG at birth is associated with a 30% to 50% reduction in neonatal mortality.^{2,7} BCG also gives protection against sepsis and respiratory infections.⁷

Reactivation at BCG site has also been witnessed in children during viral infections such as measles and human herpes virus type 6.^{8,9} However, reactivation of BCG scars has commonly associated with Kawasaki disease (KD), and suggested by many pediatricians as a diagnostic tool for KD.¹⁰ A study from Singapore, where BCG is universally given at birth, reported that 43% of patients with KD had reactivation at the BCG scar site.⁹ The study indicated that BCG site reactivation was in direct correlation with time gap between BCG vaccination and onset of KD. Shorter the duration more chances of reactivation.⁹ This could possibly explain why we only observed reactivation in the most recent BCG scars. As expected, MIS-C had behaved similar to KD in many aspects from clinical and laboratory diagnostic criteria to less common manifestations such as BCG scar reactivation.¹¹ However, the pathophysiology of MIS-C is still unknown.¹¹ The local reaction was attributed to cross-reactivity between BCG microbial components persisting at the site of vaccination and SARS-CoV-2 vaccines. In favour of the above proposed hypothesis there are evidence of eight BCG derived peptides with significant sequence homology to either SARS CoV-2 non-structural protein 3 (NSP3) or non-structural protein 13 (NSP 13) derived peptides were recently identified.¹² Similarly, reactivation of the BCG scar experienced by two health care workers after

mRNA vaccination might therefore have been caused by an immunological reaction due to the cross reactivity between BCG and SARS-CoV-2.¹³ This phenomenon in KD has been attributed to immunological cross-reactivity of mycobacterial heat shock protein (HSP) 65 with human homologue HSP 63.5. Likely mechanism may be proposed in our case as a cause for reactivation at BCG site in a case of MIS-C.

CONCLUSION

Any child with irritability and persisting fever (>3 days) not responding to antipyretics should be suspected to have MIS-C in this Covid era. All criteria need not be fulfilled; incomplete MIS-C may be presentsimilar to incomplete Kawasaki disease.⁴ In view of risk higher incidence of coronary involvement in infancy, an early diagnosis and prompt treatment are essential. Erythema at the site of BCG inoculation is rare, but it is a specific sign of Kawasaki disease and so seems to be with MIS-C. Hence, it can be used as a tool for an early diagnosis in places where it takes time to get investigations report and in resource poor settings. Children have been diagnosed early by looking at the BCG scar on admissionlike its counterpart Kawasaki disease.¹⁴ This should be particularly useful in countries where BCG vaccination is universal.

REFERENCES

1. Dufort EM, Koumans EH, Chow EJ, et al (2020) Multisystem inflammatory syndrome in children in New York State. *New Engl J Med*. 383:347-358.
2. Higgins JP, Soares-Weiser K, Lopez-Lopez J, et al (2016) Association of BCG, DTP, and measles containing vaccines with childhood mortality: systematic review. *Bmj*.355:1-13.
3. Organization W. Global COVID-19 clinical platform: case record form for suspected cases of multisystem inflammatory syndrome (MIS) in children and adolescents temporally related to COVID-19, 01 June 2020 [Internet]. Apps.who.int. 2022 [cited 2 April 2022]. Available from: <https://apps.who.int/iris/handle/10665/332236>.
4. Newburger J, Takahashi M, Gerber M, et al (2004) Diagnosis, treatment and long term management of Kawasaki Disease. *Circulation*.110:2747-2771.
5. Roth A, Gustafson P, Nhaga A, et al (2005) BCG vaccination scar associated with better childhood survival in Guinea-Bissau. *Int J*

- Epidemiol.34(3):540-547.
6. Scholtz-Buchholzer F, Berendsen M, Roth A, et al (2020) BCG skin reactions by 2 months of age are associated with better survival in infancy: a prospective observational study from Guinea-Bissau. *BMJ Global Health*.5(9):e002993.
 7. Biering-Sørensen S, Aaby P, Lund N, et al (2017) Early BCG-Denmark and Neonatal Mortality Among Infants Weighing <2500 g: A Randomized Controlled Trial. *Clin Infect Dis*.65(7):1183-1190.
 8. Muthuvelu S, Lim K, Huang L, et al (2019) Measles infection causing Bacillus Calmette-Guérin reactivation: a case report. *BMC Pediatr*.19(1):251.
 9. Loh ACE, Kua PHJ, Tan ZL (2019) Erythema and induration of the Bacillus Calmette-Guérin site for diagnosing Kawasaki disease. *Singapore Med J*.60(2):89-93.
 10. Rezai MS, Shahmohammadi S (2014) Erythema at BCG inoculation site in Kawasaki disease patients. *Mater Sociomed*.26(4):256-260.
 11. Jiang L, Tang K, Levin M, et al (2020) COVID-19 and multisystem inflammatory syndrome in children and adolescents. *Lancet Infect Dis*.20(11):e276-e288.
 12. Eggenhuizen P, Ng B, Chang J, et al (2021) BCG Vaccine Derived Peptides Induce SARS-CoV-2 T Cell Cross-Reactivity. *Frontiers in Immunology*.12:692729.
 13. Mohamed L, Madsen A, Scholtz-Buchholzer F, et al (2021) Reactivation of BCG vaccination scars after vaccination with mRNA-Covid-vaccines: two case reports. *BMC Infectious Diseases*. 21(1):1264.
 14. Cheng YW, Wong LM, So KT (2003) Update on Kawasaki disease in Hong Kong. *HK Pract*.25:127-133.
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