*Case Report*

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# 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 seencases 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 feverwhich 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 pealing 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 abouthuman 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.

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Covid-19 even had varied effects on the foetus of 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 infuenza 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 suggestingbronchiolitis as in figure 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 antibodysent.[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 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 andtemperature 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.

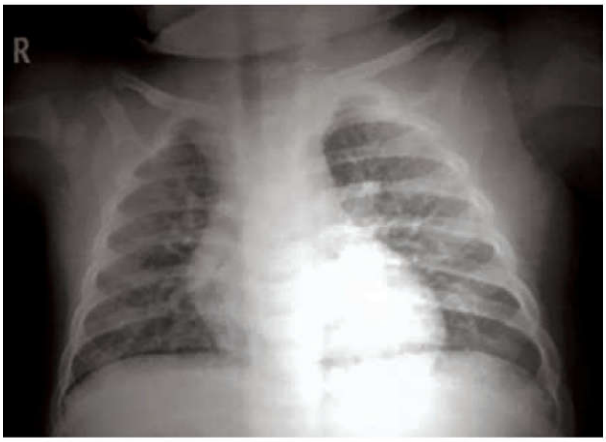


**Fig. 1:** Chest X-ray suggestive of Bronchiolitis.

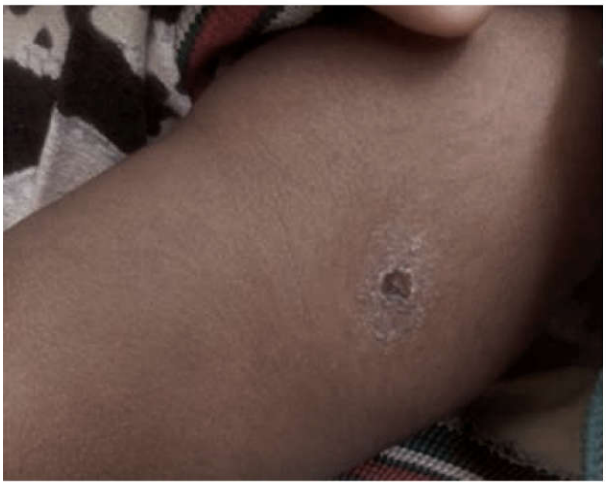

**Fig. 3:** Healing at BCG reactivation site 1 week after IVIG treatment.

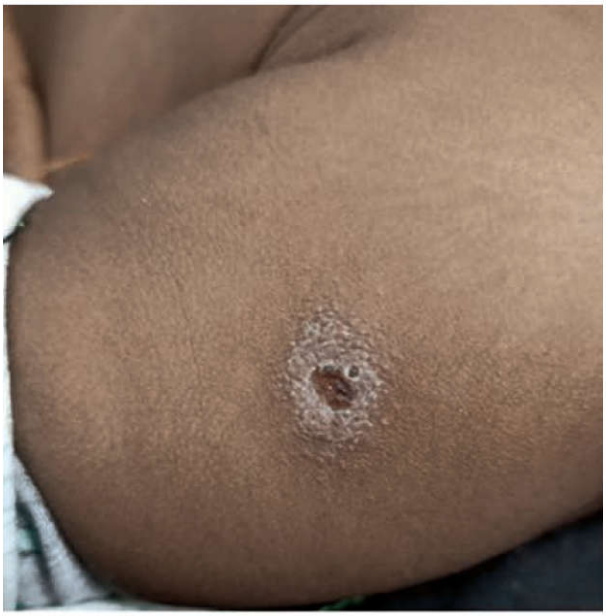

**Fig. 2:** BCG site reactivation.

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.

**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 | 3.58×105 /cumm | 2-5.5×105 /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) |

## DISCUSSION

Infections with SARS-CoV-2 in pediatric age 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 cardiacinvolvement.[3] World Health Organization and the Centers for Disease Control and Prevention (CDC), have defined the diagnostic criteria of MIS-C. [Table 2]

**Table 2:** Multi-system Inflammatory Syndrome in Children (MIS-C): WHO Definition [3]

| | |
|---|---|
| **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 | |

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

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