

Isolated remote site musculoskeletal *Mycobacterium bovis* infections after BCG immunisation in immunocompetent children

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Dear Editor,

The Bacillus Calmette–Guerin (BCG) vaccine, derived from wild-type *Mycobacterium bovis*, is administered in an attenuated form to prevent *Mycobacterium tuberculosis* (MTB) infections in children residing in endemic regions. Since the introduction of the Singapore Tuberculosis Elimination Programme in 1997—specifying mandatory BCG-immunisation at birth—the incidence fell drastically to 32.6 per 100,000 population in 2021,¹ with the paediatric population contributing 2.1% of infections.²

The vaccine is generally safe, but post-immunisation *M. bovis* infections (MBI) can occur, most commonly at the inoculation site forming localised MBI (L-MBI) such as cutaneous nodules, abscesses and lymphadenitis in immunocompetent children.³ MBI resolves spontaneously without the need for treatment with oral anti-TB drugs or surgery.⁴ Disseminated MBI (D-MBI) is rare and usually affects immunocompromised children in multiple sites including bones, joints, central nervous system, liver, spleen and lymph nodes. D-MBI also causes systemic complications of fever, weight loss, lymphadenopathy, hepatosplenomegaly and death.⁵

A third presentation variation described is the single site MBI (S-MBI), which affects a specific location remote from inoculation, without the presence of L-MBI or D-MBI, and has no correlation to the inoculation site. S-MBI involvement of the bone is estimated to occur in one per million vaccinations and affects the lower limbs, axial skeleton, upper limbs and multiple bones in decreasing frequency.^{6,7} It is thought to occur through haematogenous dissemination and is seen as a lytic lesion in the metaphysis of the long bone, with low or the absence of inflammatory markers. Treatment regimens are highly varied, ranging from anti-TB drugs, chemotherapy and surgery, to undergoing no treatment at all. Musculoskeletal S-MBI in immunocompetent children is rare, and limited evidence-based literature is available

describing its presentation and treatment. In this study, we aim to report the clinical characteristics of extremity bone and soft tissue S-MBI in immunocompetent children.

A retrospective review of children diagnosed with S-MBIs in a tertiary level paediatric hospital between 2017 and 2022 was performed with approval of the hospital ethics board. The inclusion criteria were children aged below 18, BCG vaccine administration following national immunisation guidelines, confirmed extremity musculoskeletal S-MBI, and absence of immunodeficiency conditions. L-MBIs were excluded. Data was collected on demographics; BCG vaccination details; S-MBI location and symptoms; and haematological, immunological and radiological investigations. Surgical details, anti-TB treatment regime, time to resolution, complications, readmissions and recurrence were recorded. Immunological tests for immunodeficiency included CD3, CD4, CD8 and CD20 levels; antibody testing for IgG, IgA, IgM and IgE levels; nitroblue tetrazolium levels; Mendelian susceptibility to mycobacterial diseases and immunological workup including interferon and gene sequence testing. MBI was confirmed through in-house laboratory mycobacterium culture or polymerase chain reaction (PCR) showing positive for *M. bovis*, and presence of acid-fast bacilli and necrotising granulomas on histology. PCR samples were sent for all patients. Mycobacterium cultures took on average 6 weeks for final results.

A total of 7 patients were included. Five were diagnosed with osteomyelitis, and 2 had deep soft tissue abscesses. The median age at presentation was 17.3 months (5.72–26.7). The median duration between symptom onset to seeking medical attention was 5 days (2–120). All reported pain, and the majority had localised swelling. Only 2 showed typical infective signs (redness and warmth), 1 had fever. All had normal immune workups. Two patients were subsequently diagnosed with thalassaemia and 1 with iron deficiency anaemia (Table 1).

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Table 1. Demographics, clinical signs, laboratory results, *Mycobacterium bovis* infection and surgery details in patient population.

Patient	1	2	3	4	5	6	7
Gender	Male	Male	Female	Female	Female	Male	Male
Age at BCG vaccination, day	3	1	1	1	1	1	1
Age at presentation, day (month)	177 (5.8)	821 (26.0)	562 (17.9)	530 (17.3)	704 (23.0)	381 (8.6)	216 (7.0)
Duration of symptoms at presentation, day	2	30	5	5	4	120	3
BCG inoculation site	Left arm	Left arm	Left buttock	Left buttock	Left buttock	Left buttock	Left buttock
BCG infection site	Left humerus	Left humerus	Right arm	Left tibia	Left ankle	Right foot	Right knee
BCG strain given	Indian strain II	Indian strain II	Japan strain	Japan strain	Japan strain	Japan strain	Unknown
TB contact	No	No	No	No	No	No	No
Medical conditions	Nil	Transient tachypnoea of newborn	Nil	Small atrial septal defect	Nil	Nil	Dietary-related iron deficiency anaemia
Pain at infection site	+	+	+	+	+	+	+
Swelling	-	+	+	-	+	+	+
Redness and warmth	-	+	+	-	-	-	-
Fever	-	-	+	-	-	-	-
Lymphadenopathy	-	-	-	-	-	-	-
Hepatosplenomegaly	-	-	-	-	-	-	-
Haemoglobin, g/dL	11.50	11.00	10.99	11.90	11.40	11.30	12.81
Total white cell count, x10 ⁹ /L	19.75	16.74	10.15	16.91	11.49	9.83	12.81
Monocytes, x10 ⁹ /L	1.78	0.84	0.91	1.86	1.26	0.49	1.14
Platelets, x10 ⁹ /L	651	509	353	606	410	354	584
C-reactive protein, mg/L	3.4	1.5	12.6	17.0	10.9	0.40	31.6
CD4, g/L	Nil	25	36.7	37.9	43.6	41.3	35.0

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Patient	1	2	3	4	5	6	7
CD8, g/L	Nil	27.4	22.9	16.1	24.4	15.0	18.0
IgM, g/L	0.45	0.84	0.32	1.10	1.61	0.43	0.60
IgE, g/L	4.10	96.60	46.60	78.00	2.50	191.00	2.40
Immune workup	Normal	Normal	Normal	Normal	Normal	Normal	Normal
AFB stain	Negative	Negative	Negative	Negative	Negative	Negative	Negative
Mycobacterium PCR	Positive	Positive	Positive	Positive	Positive	Positive	Positive
Mycobacterium culture	M. bovis	M. bovis	M. bovis	M. bovis	M. bovis	M. bovis	M. bovis
Histology	AFB, necrotising granulomatous inflammation	Necrotising granulomas	Necrotising granulomatous inflammation	Necrotising granulomas	Necrotising granulomas	AFB, necrotising granulomatous inflammation	AFB, granulomatous inflammation
Type of infection	Bone	Bone	Soft tissue	Bone	Bone	Bone	Soft tissue
No. of surgeries	1	1	4	1	1	2	5
Mycobacterial drug treatment	RHEL 2 months, then RH 7 months	RHEL 4 months, RE 8 months	RHEL 12 months (recurrence after 1 month of treatment)	RHEZ 2 months, RE 7 months	RHEZL 3 months, then RH 7 months	RHEZ 2 months, RH 5 months (recurrence after 7 months of treatment), RHE 2 months, RHE 5 months	RHEL 3 months REL 6 months (recurrence after 1 month of treatment)
Drug complications	Nil	Nil	Nil	Nil	Nil	Z-induced transaminitis	Isoniazid resistance
Re-infections	No	No	Yes	No	No	Yes	Yes
Time to recurrence, day	Nil	Nil	30	Nil	Nil	236	27
Follow-up complications	No	No	No	No	No	No	No

R: Rifampicin; E: Ethambutol; H: Isoniazid; L: Levofloxacin; Z: Pyrazinamide
+: present; -: absent; AFB: acid-fast bacilli; BCG: Bacillus Calmette-Guerin; CD4: cluster of differentiation 4; CD8: cluster of differentiation 8; IgM: immunoglobulin M; IgE: immunoglobulin E; MBI: *Mycobacterium bovis* infection; MSMD: Mendelian susceptibility to mycobacterial diseases; PCR: polymerase chain reaction; TB: tuberculosis
Immunological tests for immunodeficiency workup included CD4 and CD8 levels; antibody testing for IgM and IgE levels; nitroblue tetrazolium levels; Mendelian susceptibility to mycobacterial diseases workup and immunological workup, which involved interferon and gene sequence testing.

The median drug treatment duration was 10 months (9–20) with Rifampicin (R), Isoniazid (H), Ethambutol (E), Levofloxacin (L) and Pyrazinamide (P) in combinations of RHEL, RHEZ or RHEZL for the first 2 to 3 months, and RH for the next 7 to 10 months (Table 1). The number of surgeries ranged from once (4 patients) to 5 times (1 patient). The median number of surgeries were 4.5 and 1 for soft tissue and osteomyelitis, respectively; and all in the former had recurrence while 1 in the latter group recurred. MBI recurrences occurred at sites different from the original. Advanced imaging, such as MRI and ultrasound, was employed for soft tissue infections, showing extensive involvement crossing multiple anatomical planes. The median time to recurrence after the last operation was 30 days (27–236). All the children were followed up for at least 24 months after the completion of anti-mycobacterial treatment, and no recurrences occurred.

The pathophysiology of MBI in immunocompetent children is unclear and presents a diagnostic challenge, making it difficult to select relevant investigations for accurate early diagnosis. In our patients, the subclinical nature and long latency (median 17.3 months) meant that a high degree of suspicion was required for diagnosis and institution of treatment. Yet, early recognition is important due to the potentially serious outcome, extended treatment period and risk of recurrences and chronicity that is complex to treat.

More severe disease and increased mortality were reported with high levels of C-reactive protein and erythrocyte sedimentation rate; there were also blood count abnormalities, including anaemia, leukopaenia, thrombocytopaenia and neutropaenia.⁸ Although we had 3 patients with anaemia, no correlation with infection severity was found. Our patients had no family history of autoimmune disease and had normal immune workups and hence deemed immunocompetent. Better characterisation of BCG-induced immune response can potentially help in understanding the variabilities in MBI occurrences. Controversy exists regarding the various hypotheses, and evidence points towards an unclassified inherited childhood immunodeficiency.^{9,10}

Several notable differences between soft tissue abscesses and osteomyelitis were evident. The former demonstrated a shorter time to recurrence, higher number of surgeries and higher rate of recurrence. The sole osteomyelitis recurrence (patient 6) was postulated to be related to non-compliance to prescribed anti-mycobacterium medication regime. We also found that while soft tissue S-MBI was localised to a

specific region, it was often poorly compartmentalised and spread to involve surrounding tissues. This was exemplified in patient 7 who had a recurrent extensive wrist abscess that crossed multiple tissue planes involving muscles, tendons and wrist joint. In such situations, treatment is largely dependent on multiple aggressive surgical debridement for clearance and source control, paired with extended medication.

Considering potential severity, we recommend mycobacterial cultures to be performed in atypical infection presentations. Early drug treatment could also be initiated in an attempt to obtain source control and limit spread. As the disease process remains poorly understood, more research on risk factors that might predict susceptibility to severe infection in immunocompetent children and treatment standardisation is needed to reduce MBI complications and improve quality of life for both children and their caregivers.

Declaration

The authors declare there are no affiliations with or involvement in any organisation or entity with any financial interest in the subject matter or materials discussed in this manuscript.

Ethics statement

The manuscript was approved by the SingHealth Centralised Institutional Review Board (CIRB 2023/2559). Waiver of consent was granted, as this was a retrospective deidentified review.

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