

# Bacillus Calmette-Guérin Adenitis: An Intriguing Series of Four Cases

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## ABSTRACT

Bacille Calmette-Guérin (BCG) vaccine is part of the immunisation schedule in India. It is a live-attenuated vaccine with very few adverse reactions, one of which is BCG adenitis. The intriguing fact is that there has been a sudden upsurge in the number of BCG adenitis cases (two males and two female children), with four reported cases within three months (March 2023-June 2023). There were two male and two female children, aged between 2-8 months. All of them presented with left axillary swelling, and all but one had low grade fever only in the initial days. They all had a healed BCG vaccination scar on their left arm. Fine Needle Aspiration Cytology (FNAC) showed multiple epithelioid granulomas and, in some cases, frank caseation necrosis with the demonstration of tubercle bacilli using either Ziehl-Neelsen (Z-N) stain or Cartridge-based Nucleic Acid Amplification Test (CBNAAT). These cases mostly benefited from pus aspiration from the swelling site, with no definite role for oral antibiotics. Proper training of nursing or paramedical staff regarding vaccination technique and dosage, proper maternal and child healthcare, early detection of these cases with a high index of suspicion, as well as adequate knowledge of the treating doctors and parents/caregivers, may help in prompt management of these cases in future occurrences.

**Keywords:** Caseation necrosis, Cartridge-based nucleic acid amplification test, Epithelioid granulomas

## INTRODUCTION

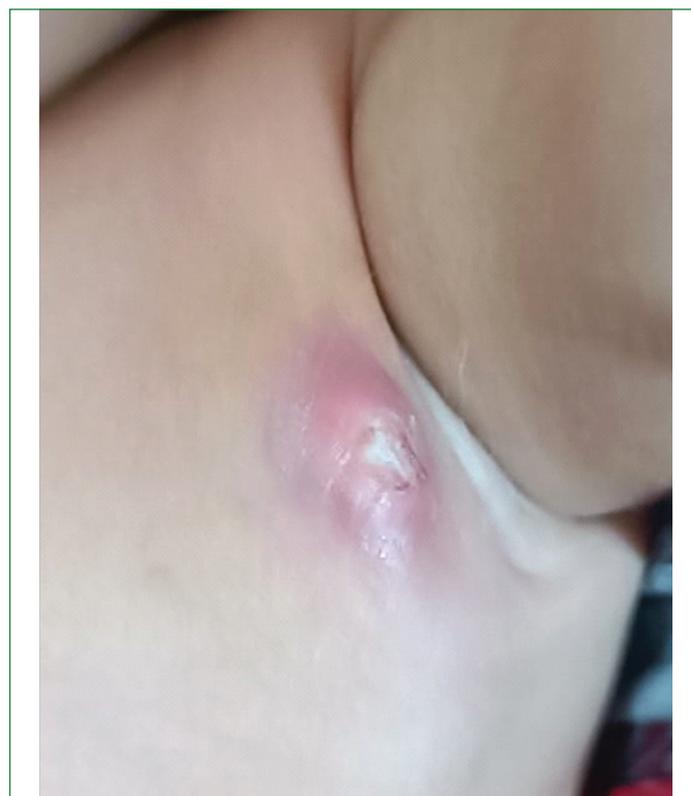
The BCG vaccine was incorporated as part of the World Health Organisation's (WHO) immunisation programme to strengthen the fight against childhood tuberculosis in developing countries [1]. It is considered a very safe vaccine with low rates of adverse reactions [2]. However, BCG adenitis is the development of ipsilateral regional lymph node enlargement following BCG vaccination [3]. After inoculation of BCG, there is rapid multiplication of live attenuated bovine mycobacteria, which are then transported to regional lymph nodes and disseminated through the blood, resulting in small foci in various organs. BCG vaccination and mild glandular enlargement are part of the normal response that corresponds with the primary complex of natural tuberculous infection. BCG adenitis is used to describe this pathological entity when this reaction is exacerbated, leading to unpleasant symptoms [4]. With proper vaccination schedules, sanitation practices, and good antenatal and postnatal care, BCG adenitis is not commonly encountered in today's medical practice. However, a few cases have been reported within a span of three months from March 2023 to June 2023, which were highlighted in the present series.

The study consisted of four cases of BCG adenitis referred from the Paediatrics clinic to the Department of Pathology for a Fine Needle Aspiration (FNA) procedure. The FNA procedure was explained to the legal guardians and performed after obtaining their consent. The local area of the swelling was cleaned with spirit, and with proper aseptic precautions, a 23 Gauge needle fitted in a cytology aspiration gun was used to aspirate material, followed by smear preparation on glass slides. A second attempt at aspiration was also made to retrieve material for CBNAAT. The air-dried smears were then stained using Leishman-Giemsa stain and Z-N stain. The reporting was based on smear findings and CBNAAT results, which were tabulated separately in a master sheet. Written consent was obtained from each legal guardian while dispatching the report, confirming their willingness to participate in the case series.

### Case 1

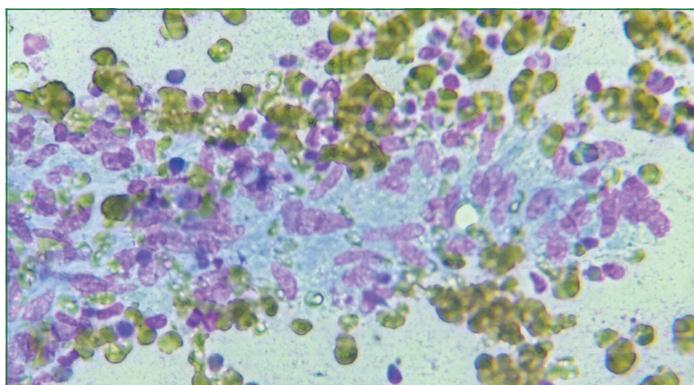
A two-month-old female child was brought to the Outpatient Department (OPD) of Paediatrics with complaints of left axillary

swelling, initially accompanied by a low-grade fever, for the last six weeks following BCG vaccination. The patient was unresponsive to oral antibiotic therapy, with a body weight of 5 kg and developmental milestones within normal limits. The BCG vaccination scar had healed with no signs of inflammation. The birth weight was 2.5 kg, and the pregnancy with labour was uneventful. The patient was referred to the FNAC clinic for aspiration from the axillary swelling for cytological study. The swelling measured (3×3) cm and was a soft swelling with features of inflammation, including erythema of the skin [Table/Fig-1]. The aspirate was pus.



**[Table/Fig-1]:** Left axillary swelling with superficial erythema and pus-point.

The cytological study showed multiple epithelioid granulomas [Table/Fig-2] in the background of lymphoid cells and necrosis. The Z-N stain was non contributory. CBNAAT was positive for tubercle bacilli. The findings were consistent with BCG adenitis. The patient was treated with multiple aspirates of pus from the site of swelling, leading to gradual remission of symptoms over a period of eight weeks. No oral antibiotic medication was prescribed at the discretion of the treating physician.

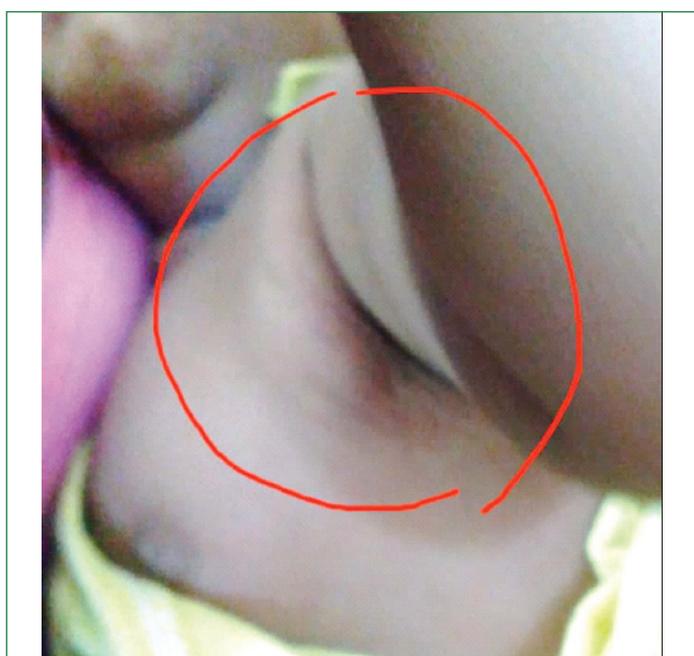


**[Table/Fig-2]:** Collection of epithelioid histiocytes in cytological smears of first case (Leishman-Giemsa stain, 100X magnification).

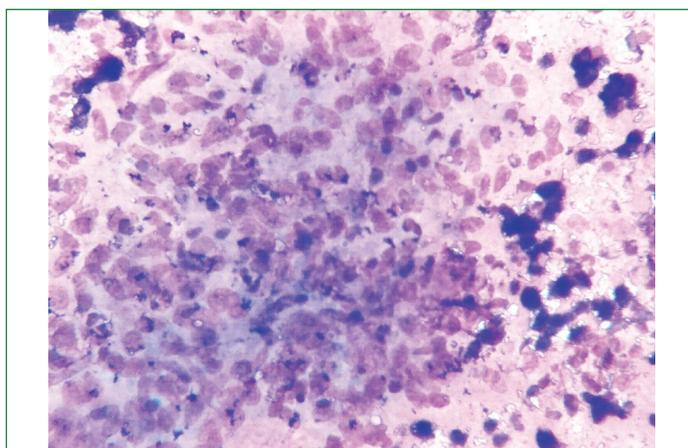
### Case 2

The parents of a three-month-old female child complained of left axillary swelling for 10 days, associated with a low-grade rise in temperature for the initial two days. Her body weight was 4.9 kg, which is lower than expected, but there was no developmental delay. A healed scar at the BCG vaccination site was observed. However, her birth weight was normal (2.9 kg), and the labour with the postpartum period was uneventful. She was advised to undergo a Complete Blood Count (CBC), which showed anaemia with a Haemoglobin (Hb) level of 7.9 gm/dL.

During the examination at the FNAC clinic, the swelling was measured at 2×2 cm and was firm [Table/Fig-3], and the aspirate was fluidic. The Leishman-Giemsa stain of the smear showed epithelioid granulomas in a background of caseation necrosis [Table/Fig-4]. The Z-N stained smear showed scanty AFB. The diagnosis was consistent with the clinical picture of BCG adenitis. The patient was prophylactically treated with Beta-lactam antibiotics, namely amoxicillin and clavulanic acid, at a rate of 50 mg/kg every eight hours for seven days. She was followed-up for six weeks, during which there was a gradual reduction in the swelling.



**[Table/Fig-3]:** Firm, 2×2 cm left axillary swelling.

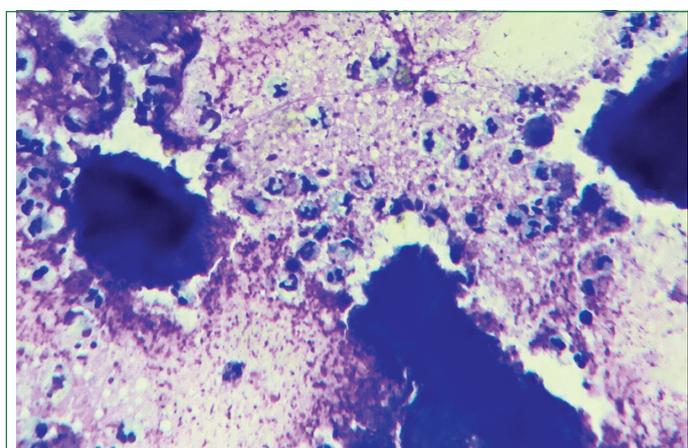


**[Table/Fig-4]:** Epithelioid granuloma in the aspirated smear (Leishman-Giemsa stain, 100X magnification).

### Case 3

An eight-month-old male child was referred from the OPD of Paediatrics with complaints of left axillary swelling persisting for six weeks, which did not resolve with multiple courses of antibiotics. There was no associated fever. An unremarkable scar was observed at the BCG vaccination site. The body weight was normal for his age (9 kg), and the developmental milestones were normal. The birth weight was also normal (3 kg), and the pregnancy was uneventful.

During the examination, the swelling measured 1×1 cm and was soft, with unremarkable superficial skin. The aspirate revealed pus, followed by a reduction in size. Stained smears showed caseation necrosis with suppurative inflammation [Table/Fig-5]. Some collections of macrophages were observed, but no well-defined epithelioid granuloma was visualised in the smears. The Z-N stain was non contributory. CBNAAT showed positivity for tubercle bacilli. The diagnosis was consistent with BCG adenitis.



**[Table/Fig-5]:** Caseation necrosis with superadded inflammation (Leishman-Giemsa stain, 100X magnification).

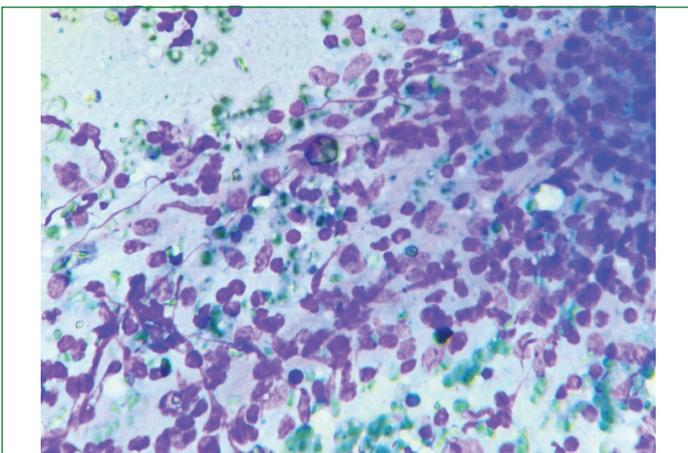
The patient was watchfully followed-up in the OPD, and complete remission was achieved within three weeks. No further medical treatment was required as the swelling reduced following pus aspiration.

### Case 4

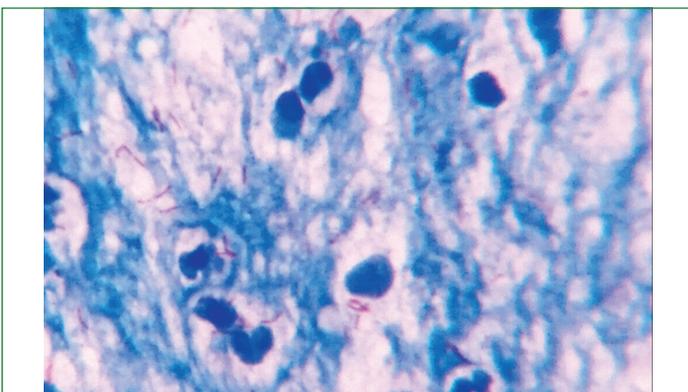
A three-month-old male child was brought to the pediatrician by his parents with symptoms of left axillary swelling persisting for one month, accompanied by low-grade fever for the initial five days. The baby weighed 6 kg, and a healed BCG vaccine scar was observed [Table/Fig-6]. The delivery was a term normal delivery, and the birth weight was 2.9 kg. On palpation, the swelling measured 2.5×2 cm with inflamed superficial skin. The aspirate consisted of blood-mixed pus. Cytology smears showed multiple epithelioid granulomas [Table/Fig-7] along with added inflammation. The Z-N stain revealed positivity for AFB [Table/Fig-8]. The diagnosis was BCG adenitis.



**[Table/Fig-6]:** Healed Bacille Calmette-Guérin (BCG) vaccination scar.



**[Table/Fig-7]:** Epithelioid granulomas admixed with lymphoid cells (Leishman-Giemsa stain, 100X magnification).



**[Table/Fig-8]:** Acid Fast Bacilli (AFB) demonstrated in Z-N stain (1000X magnification).

The patient was treated with incision and drainage, along with a course of Beta-lactam antibiotics (amoxicillin and clavulanic acid at a rate of 50 mg/kg every eight hours for five days). Within eight weeks, complete remission was achieved. All the above findings have been summarised in the table below [Table/Fig-9].

## DISCUSSION

The BCG vaccine is a live-attenuated form of *Mycobacterium bovis*, with the presence of multiple strains such as Pasteur strain 1173, Danish strain 1331, Glaxo strain 1077, etc. The vaccine is administered at a concentration of 50 thousand to three million live particles per dosage [5]. There are several factors that can influence the complications associated with BCG vaccination, including vaccine strains, immunisation techniques, dose, immunity, and the physique of the child [6]. These complications can be classified into mild and severe forms. Mild complications include regional lymphadenitis, cutaneous lupoid reactions, and eczema, while severe forms include suppurative lymphadenitis, osteomyelitis, and disseminated BCG infections. The incidence of all these cases is extremely low in the current scenario [7,8]. Among them, BCG vaccine-induced suppurative adenitis is the most common severe complication [9]. The decrease in the incidence of all severe reactions may be attributed to a better immunisation schedule, improved maintenance of the vaccine cold chain, and enhanced antepartum and postpartum care, leading to improved maternal and child health.

However, there has been a sudden increase in cases of BCG adenitis, with four cases occurring within a span of three months in the current setting. The male-to-female ratio (M:F) in these cases was 1:1, and the age ranged from 2 to 8 months. According to larger population data, the majority of cases occur in male infants within the first six months of age [10]. All these babies had uneventful deliveries, normal birth weights, and no developmental delays. Their body weights were appropriate for their age, except for the second case, who was also anaemic.

All of these cases were unresponsive to oral antibiotics and presented with severe complications, including suppuration and pus aspiration. Most of them benefited from pus aspiration or incision and drainage, which were often supplemented with oral Beta-lactam antibiotics to prevent secondary infections. However, there are differences of opinion regarding the use of oral antibiotics in these cases. Different treatment strategies for BCG-induced adenitis have been reported, including a "watch and see" approach with follow-up [11], anti-tubercular treatment [12], needle aspiration with or without isoniazid instillation, incision and drainage [13], and surgical excision

Case no.	Age (in months)	Gender	Birth weight (in kg)	Symptoms	Preprocedural treatment and investigations	On examination and nature of aspirate	Cytology findings	Z-N stain and CBNAAT	Follow-up
1.	2	Female	2.5	Fever for one week, left axillary swelling for six weeks Body weight- 5 kg	Oral antibiotics with no response	3x3 cm soft left axillary swelling with erythematous skin Aspirate- pus	Multiple epithelioid granulomas in background of lymphoid cells and necrosis	Z-N stain- non contributory CBNAAT- positive	Multiple pus aspirates with reduction of symptoms over eight weeks
2.	3	Female	2.9	Fever for two days, left axillary swelling for 10 days Body weight- 4.9 kg	CBC- Anaemia with Hb=7.9 gm/dL	2x2 cm, firm left axillary swelling Aspirate- fluidic	Epithelioid granulomas in a background of caseation necrosis	Z-N stain- AFB positive	Beta-lactam antibiotics with gradual reduction of the swelling over six weeks
3.	8	Male	3.0	Left axillary swelling for six weeks Body weight- 9 kgs	Multiple course of antibiotics with no response	1x1 cm, soft left axillary swelling Aspirate- pus with reduction in size of the swelling	Caseation necrosis with suppurative inflammation, few collection of macrophages seen	Z-N stain- non contributory CBNAAT- positive	Remission of symptoms over three weeks
4.	3	Male	2.9	Fever for five days with left axillary swelling for one month Body weight- 6 kg	--	2.5x2 cm swelling in left axilla with inflamed superficial skin Aspirate- blood-mixed pus	Multiple epithelioid granulomas admixed with super-added inflammation	Z-N stain- AFB positive	Incision and drainage with Beta-lactam antibiotics followed by remission over eight weeks

**[Table/Fig-9]:** Distribution of the cases based on their demographic characteristics, presentation, investigations and treatment.

CBC: Complete blood count; Hb: Haemoglobin; Z-N: Ziehl-Neelsen; CBNAAT: Cartridge-based nucleic acid amplification test; AFB: Acid fast bacilli

of involved lymph nodes [14], among others. However, the standard form of treatment followed in the study conducted by Govindarajan KK and Chai FY aligns with the protocol followed in the present case series [15]. Previous studies have also shown that oral erythromycin and antitubercular drugs do not hasten regression or prevent progression into suppuration [16]. Needle aspiration has been found to be effective in treating small swellings or suppuration, but surgical removal of enlarged lymph nodes has been seen as effective in difficult cases [17]. A high index of clinical suspicion is essential for proper and timely diagnosis in recently vaccinated children [18].

While exploring the possible reasons behind the rising cases, multiple factors may come into play. Poor antenatal care resulting in low birth weight and subsequent low immunity of the child with an exaggerated BCG reaction could be one contributing factor. Other factors may include inadequate training of staff administering the vaccine, improper dosage, or inadequate maintenance of the vaccine cold chain, leading to altered efficacy. In a recent study conducted by Hassanzad M et al., there have been speculations about the possible role of genetic polymorphism of cytokines such as Tumour Necrosis Factor- $\alpha$  (TNF) and Interleukin (IL-10) in the occurrence of BCG adenitis in certain ethnic groups, even in otherwise healthy infants [19].

A comprehensive evaluation of all the aforementioned factors needs to be taken into consideration for the prevention of this adverse reaction. It is also crucial to raise awareness among paramedical staff regarding this condition and provide them with proper training. One of the main limitations in the present case is the lack of standardised diagnostic criteria and treatment protocols thus far [20]. Therefore, it is necessary to combine knowledge from existing literature to develop appropriate diagnostic criteria and therapeutic protocols for the management of these cases.

## CONCLUSION(S)

The BCG vaccine is generally considered very safe, with minimal adverse reactions. Currently, there are very few reported cases of BCG adenitis due to proper staff training. However, the present case series highlights a sudden surge in the number of BCG adenitis cases in the study setting, with four reported cases within three months. This emphasises the need for prompt intervention, as well as training and awareness among healthcare providers, to prevent such occurrences in the future.

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