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CASE REPORT

Bacille Calmette–Guerin Lymphadenitis in Infants: A Lesser Known Entity – Report of two Cases

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Bacille Calmette–Guerin (BCG) vaccine containing live-attenuated *Mycobacterium bovis* was first used in humans to prevent tuberculosis (TB) in 1921. Intradermal BCG vaccine gives rise to classic primary complex that consists of a cutaneous nodule at the site of injection and subclinical involvement of the regional lymph nodes, which is self-limiting and requires no treatment. BCG lymphadenitis is the most common complication of BCG vaccination. Fine-needle aspiration is the rapid, safe, and cost-effective method for diagnosis as well as the management of BCG lymphadenitis. Awareness of this lesser known entity is important to prevent misdiagnosis. We report two cases of 2½ month and 6-month healthy male infants with left axillary lymphadenopathy following BCG vaccination. Fine-needle aspiration from both the cases revealed features of necrotizing granulomatous lymphadenitis with Ziehl-Neelsen stain for acid-fast bacilli being positive in 2nd case. Ipsilateral regional lymph node enlargement following BCG vaccination is considered as the most common complication, some progress to suppuration. Very rarely disseminated BCG infection may develop in immune-compromised individuals, resulting in a devastating outcome. Variable strategies have been applied in treating lymphadenitis related to BCG vaccine in the past decade, ranging from observation, antimycobacterial therapy, aspiration, incision, and drainage to lymph node surgical excision.

Key words: Bacille Calmette–Guerin, fine-needle aspiration, lymphadenitis, Ziehl-Neelsen stain, infants

INTRODUCTION

The Bacille Calmette–Guerin (BCG) vaccine is a live-attenuated vaccine with residual virulence. After the first introduction of BCG vaccine in 1921, it was incorporated in expanded program of immunization in 1974 by the World Health Organization to decrease the serious complications and mortality of tuberculous infection.[1] In India, BCG is routinely administered intradermal at left deltoid region to newborns under National Immunization Program. Although BCG is a safe and widely accepted vaccine, it sometimes causes local adverse reaction such as regional lymphadenitis, local abscess formation, osteomyelitis, and rarely disseminated mycobacterial infection.[2]

BCG-induced lymphadenitis is the most common complication of BCG vaccination. Fine-needle aspiration (FNA) being a rapid minimally invasive test can help in proper diagnosis and the patient can be observed/managed appropriately rather than treated with antitubercular medication.[3] We hereby report two cases of BCG lymphadenitis in young infants.

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CASE REPORTS

Case 1

A 6-month-old male child presented with swelling over left axillary region for 3 weeks. On examination, he had a swelling of size 2 × 2 cm with overlying skin being slightly reddish. No other lymphadenopathy or hepatosplenomegaly was noted. No family history or TB contact history was present. Ultrasonography showed a hypoechoic lesion of 4 × 4 × 2 cm with no internal vascularity, possibly intramuscular hematoma/abscess. The patient had been given BCG vaccination on D2 of life, and there was no significant

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lesion in the left deltoid region currently [Figure 1]. FNA from the swelling was done.

Case 2

A 2½ month male child presented with complaints of left axillary swelling for 1 month. On examination, he had a swelling of 2 × 1.5 cm with overlying skin being unremarkable. No family history or TB contact history was present. Chest X-ray showed an isodense lesion in left axillary region with no lung involvement. Systemic examination was normal. He had a history of BCG vaccination in left arm on D2 of life. No other significant complaints were noted [Figure 1]. FNA of the swelling was advised.

Non-guided FNA of the swelling in both the cases was done using 23g needle and aspirate of 1 ml and 1.5 ml pus-like material following which the swelling slightly subsided. Sample was taken for toluidine blue, Giemsa, Pap, and Ziehl–Neelsen (ZN) stains. Cytosmears were adequate with abundant thick necrosis, many neutrophils, lymphocytes, histiocytes, and degenerating cells seen. There were numerous epithelioid cell granulomas, histiocytic aggregates, and granulation tissue fragments [Figures 1 and 2]. ZN stain for acid-fast bacilli was positive in 2nd case. Final report in both the cases was given as necrotizing granulomatous lymphadenitis; morphology compatible with BCG lymphadenitis. In both the cases, the parents sputum samples were tested negative for *Mycobacterium tuberculosis* (TB) by ZN staining and GeneXpert. After 3 months, the ipsilateral nodes had resolved spontaneously and are currently on follow-up.

DISCUSSION

The history of the BCG vaccine starts with Albert Calmette and Camille Guerin. They were two French scientists who from 1905 had been working on developing a vaccine against TB. BCG is an abbreviation of Bacillus Calmette–Guerin, meaning the bacilli of Calmette and Guerin. Between 1905 and 1918, Calmette and Guerin carried out research into the mechanisms of TB infection. By 1921, the tubercle bacillus had been subcultured 230 times and it was so weakened that it was believed that it could confer immunity without causing disease in humans.[4]

Original BCG vaccine is a live-attenuated form of *Mycobacterium bovis*. World Health Organization established the "Expanded Program on Immunization" in 1974 to ensure that all children have access to routinely recommended vaccines including BCG. Each year 120 million doses of BCG vaccine are administered worldwide. Most of the presently used BCG vaccines are the different strains of *M. bovis* – Pasteur 1173 P2, Danish 1331, Glaxo 1077, and Tokyo 172, accounting for approximately 90% of all used BCG vaccines worldwide.[2,4]

BCG vaccination is done by intradermal inoculation of 0.05 ml vaccine at left deltoid region (In India). It causes erythematous induration at the site of inoculation, which follows pustule formation after 2–3 weeks; ulceration, drainage, and crusting at 4–6 weeks after vaccination. Healing occurs with small residual scar 10–12 weeks after vaccination.[5]

Reported incidence of BCG vaccine-related complications varies from 0.1% to 17% in different studies worldwide. BCG-related lymphadenitis is the most common complication

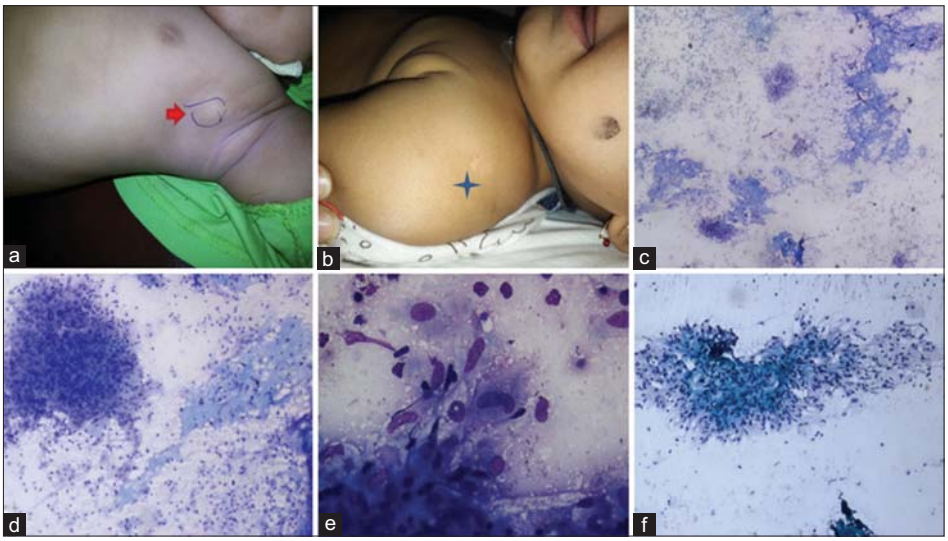

Figure 1: (a) Well-defined swelling over left axilla measuring 2 cm × 2 cm (arrow); (b) previous scar mark of Bacille Calmette–Guerin vaccination site (star); (c-f) cytosmears showed abundant thick necrosis, many neutrophils, lymphocytes, along with numerous epithelioid cell granulomas, histiocytic aggregates, and granulation tissue fragments (toluidine blue, Giemsa, Pap, ×400)

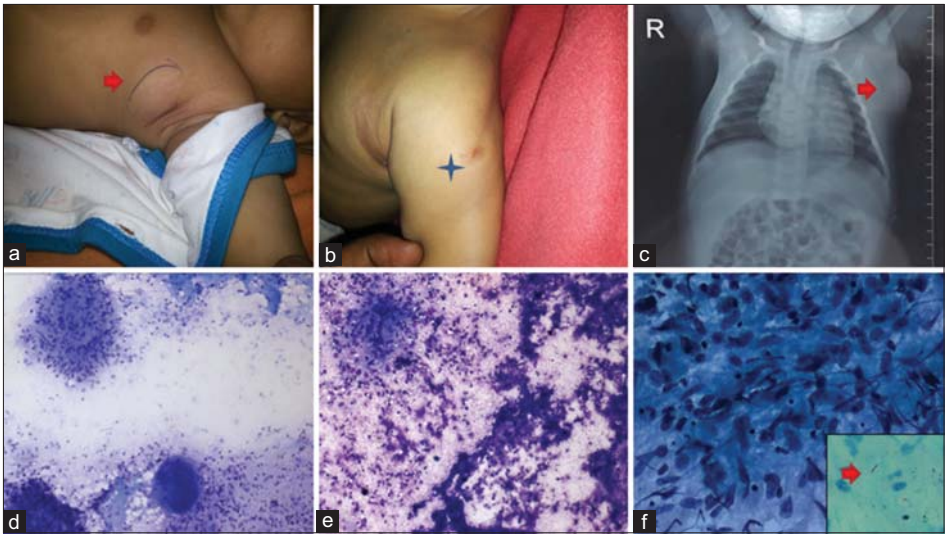

Figure 2: (a) Swelling over left axilla measuring 2 cm × 2 cm (arrow); (b) Previous scar mark of Bacille Calmette–Guerin vaccination site (star); (c) Chest X-ray showed an isodense lesion (arrow) in left axillary region with no lung involvement; (d and f) microscopy showed numerous epithelioid cell granulomas, histiocytic aggregates in a background of abundant thick necrosis, neutrophils, and lymphocytes (toluidine blue, Giemsa, Pap, ×400), beaded rod shape bacilli was seen (Inset) (Zheil–Neelson, ×1000)

of BCG vaccination.[2] BCG regional lymphadenitis is related to either of the following: (a) host-related factors, i.e., very early age of the patient, congenital or acquired immunodeficiency; (b) factors related to administration, i.e., subcutaneous instead of intradermal, higher dose; or (c) related to vaccine strain, i.e., residual virulence of the BCG substrain, type of vaccine, and viability of final vaccine product. Immunologically, normal newborn has double the incidence of BCG adenitis compared with older infants and children.[2,6]

Various studies have shown slightly male predominance with predominant age of presentation being 2–6 month and maximum size of lymph node ranging from 1 to 3 cm.[2,3,6]

The term BCG lymphadenitis applies when lymph node(s) have become large enough to be easily palpable and a cause of concern for the parents, likely with a diameter ≥ to 1 cm.[1] It can be of two types:

1. Regional lymphadenitis

The following features are in favor of regional BCG-related lymphadenitis rather than other pathologies (a) BCG vaccination at the ipsilateral arm, (b) onset between 2 weeks and 6 months, (c) child age not more than 2 years, (d) absence of systemic manifestations such as fever and weight loss, (e) absence of tenderness over the lymph node(s), and (f) axillary lymph node is mostly involved, although supraclavicular or cervical may be involved in isolation or in association with axillary lymphadenopathy. Laboratory and radiological investigations are not routinely recommended in a thriving child with unremarkable physical examination and no evidence of immunodeficiency in the family history.[1]

**Nonsuppurative lymphadenitis*

This form represents the majority of BCG-related lymphadenitis. Its typically develops 2 weeks to 6 months postimmunization and tends to affect the axillary lymph node(s).

**Suppurative lymphadenitis*

The suppurative form is marked by the progressive enlargement of regional lymph node (s) with collection of suppurative material and fluctuation associated with erythema and edema. If untreated, suppurative lymphadenitis frequently ruptures with sinus formation, resulting in prolonged course of illness and scaring sequels.[3]

2. Disseminated BCG infection/Disseminated/ Systemic BCG disease/BCGosis

There is involvement of distant anatomical site(s) beyond BCG administration site and ipsilateral lymph node(s). Disseminated BCG infection is the most serious complication of BCG vaccination. Fatal infection has occurred at a rate of 0.06–1.56 cases per million doses; these deaths occurred primarily among immune-compromised persons. Disseminated BCG is commonly seen in primary immunodeficiency (PID) including severe combined immunodeficiency, complete Di George syndrome, chronic granulomatous diseases, the Mendelian susceptibility to mycobacterial disease (e.g., interferon-g receptor 1/2 deficiencies, IL-12/23 receptor b1 chain deficiency, IL-12p40 deficiency, S TAT1 deficiency

and NEMO deficiency, and acquired immunodeficiency syndrome.[7,8]

Diagnosis of BCG lymphadenitis depends on the history and clinical examination. Cases are diagnosed as ipsilateral enlargement of local lymph node at the site of BCG vaccination in the absence of any constitutional symptoms with other identifiable cause of adenitis. A tuberculin skin test is not useful for making a diagnosis of BCG lymphadenitis with typical presentation. The test is expected to be positive after recent BCG vaccination in immunocompetent host. However, it can be supplemented by a negative interferon-gamma release assay (IGRA) for *M. tuberculosis*, together with a normal chest radiograph might help in diagnosis by excluding TB in the rare situation of BCG lymphadenitis presenting atypically as an isolated left cervical mass without concomitant axillary involvement. The point to note over here is negative predictive value of IGRA and its utility in infants to exclude infection by *M. tuberculosis* remains controversial, and overreliance on the test in this young age group is discouraged. A negative tuberculin test should raise the suspicion of PID condition.[9]

BCG lymphadenitis is often difficult to differentiate from tuberculous lymphadenitis. Isolated axillary lymphadenitis of tuberculous etiology is very rare entity. Routine investigations such as blood examination, chest X-ray, and Mantoux test have no role in diagnosis. Microbiological separation of BCG is confirmatory, but species identification of acid-fast bacilli often needs phage typing or genetic analysis.[10]

Antimycobacterial drugs cannot prevent suppuration nor shorten the duration of healing, therefore are not recommended. Repeated aspirations are required for optimal management with a wider bore needles for ease of evacuation of thick inflammatory material. Needle aspiration is considered to be a safer option when compared with surgical excision, which likely will require general anesthesia in young infants.[1] S. Abbas Banani and Alborzi concluded that surgical excision is recommended in nonhealing cases after three attempts of aspiration.[2,11] Incision and drainage should be avoided in cases of suppurative BCG lymphadenitis due to the risk of persistent draining wound, delayed wound healing, and unpleasant cosmetic outcome with scar formation.[1,2]

CONCLUSION

Nonsuppurative BCG lymphadenitis is a relatively common benign condition that will regress spontaneously over a matter of weeks to months. A high index of clinical suspicion for BCG lymphadenitis should be kept in mind for patients who are recently vaccinated. FNA cytology combined with clinical correlation is useful not only in approaching at diagnosis but also in management. Multiple aspirations can be done to hasten the resolution by emptying its content and also provide material for appropriate microbiological investigations. Complete surgical excision should be considered for failed needle aspiration or recurrence of suppuration despite repeated aspirations. The addition of antimicrobial therapy or incision/drainage is of no proven benefit. Awareness, surveillance, and generation of data on complications at the vaccination centers are very important.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the legal guardian has given his consent for images and other clinical information to be reported in the journal. The guardian understands that names and initials will not be published and due efforts will be made to conceal patient identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Nagi E, Dayel A, Alshehri M, Alzahrani M, Sami A, Suliman A, *et al*. Bacillus Calmette Guerin vaccine related lymphadenitis in children: Management guidelines endorsed by the Saudi Pediatric Infectious Diseases Society (SPIDS). Int J Pediatr Adolesc Med 2015;2:89-95.
2. Pal S, Chakarabarti S, Phukan JP, Biswas S, Sinha A, Sinha R, *et al.* Role of needle aspiration in diagnosis and management of suppurative Bacille Calmette-Guerin adenitis: An institutional study of 30 cases. J Lab Physicians 2015;7:21-5.
3. Bukhari E, Alzahrani M, Alsubaie S, Alrabiaah A, Alzamil F. Bacillus Calmette-Guerin lymphadenitis: A 6-year experience in two Saudi hospitals. Indian J Pathol Microbiol 2012;55:202-5.
4. Luca S, Mihaescu T. History of BCG vaccine. Maedica (Buchar) 2013;8:53-8.
5. Park K, editor. Epidemiology of communicable diseases. In: Park's Text Book of Preventive and Social Medicine. 23rd ed. New Delhi: Bhanot Publishers; 2015. p. 196-8.
6. Behjati B, Ayatoallahi J. Post BCG lymphadenitis in vaccinated infants in Yazd, Iran. Iran J Pediatr 2008;18:351-6.
7. Al Jumaah S, Al Hajjar S, Al Mousa H. Bacille Calmette-Guérin vaccination in Saudi Arabia: Benefits versus risks. Ann Saudi Med 2012;32:1-3.
8. Sohail S, Afzal M, Anwar V, Shama Q. Disseminated

bacille calmette-guerin (BCG) disease in an infant with severe combined immunodeficiency. J Coll Physicians Surg Pak 2014;24 Suppl 3:S259-61.
9. Chan WM, Kwan YW, Leung CW. Management of Bacillus Calmette-Guerin lymphadenitis. Hong Kong J Paediatr 2011;16:85-94.
10. Goraya JS, Virdi VS. Bacille Calmette-Guérin lymphadenitis. Postgrad Med J 2002;78:327-9.
11. Banani SA, Alborzi A. Needle aspiration for suppurative post-BCG adenitis. Arch Dis Child 1994;71:446-7.