

## REVIEW

## Bacille Calmette-Guérin lymphadenitis

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Bacille Calmette-Guérin (BCG) lymphadenitis is the most common complication of BCG vaccination. Two forms of BCG lymphadenitis can be recognised in its natural course—simple or non-suppurative lymphadenitis, which usually regresses spontaneously over a period of few weeks, and suppurative BCG lymphadenitis distinguished by the development of fluctuations in the swelling, with erythema and oedema of overlying skin. Healing in suppurative glands occurs through spontaneous perforation and sinus formation, followed by closure of the sinus by cicatrization. Non-suppurative BCG lymphadenitis is best managed with expectant follow ups only, because medical treatment with erythromycin or antituberculous drugs do not hasten the regression or prevent development of suppuration. Suppurative BCG lymphadenitis may be treated by needle aspiration to hasten resolution and prevent spontaneous perforation and sinus formation. Surgical excision is rarely needed and is meant for cases of failed needle aspiration or for draining BCG nodes.

regional lymph glands, followed by the haematogenous dissemination of the BCG, resulting in creation of very small foci in different organs. This is also called “normal BCG-itis” in the course of successful BCG vaccination.<sup>3</sup> The reaction at the site of vaccination and the glandular response together constitute the primary complex produced by the infection with BCG, an experimental equivalent of primary complex of natural tuberculous infection in the lungs.<sup>5,6</sup> It follows that the development of pathological reactions at the site of inoculation and in the regional nodes after BCG injection is expected and is without any ill effects unless it becomes severe and unpleasant.<sup>5,6</sup> Slightly enlarged regional nodes are, therefore, common after BCG vaccination, but are rarely noticeable unless searched for specifically. This subclinical lymphadenitis regresses spontaneously, is of no practical importance, and may not be regarded as a complication.<sup>4,5</sup> However, there is no easy way to differentiate “normal” from “abnormal” and there is no agreed definition as to what constitutes BCG lymphadenitis, particularly with regards to the size of lymph node enlargement, and its onset after vaccination.<sup>5,7–10</sup> It has been recommended that the term BCG lymphadenitis be used to refer to the cases where lymph nodes have become large enough to be easily palpable and a cause of concern for the parents.<sup>5,6</sup>

Though BCG lymphadenitis may develop as early as two weeks after vaccination, most of the cases appear within six months, and almost all cases occur within 24 months.<sup>5–7,11</sup> Ipsilateral axillary glands are involved in more than 95% of the cases, though supraclavicular or cervical glands may occasionally be enlarged in isolation or in association with enlarged axillary nodes.<sup>5,6,11,12</sup> In majority of the cases there are only one or two enlarged nodes, though multiple glands may be palpable in some cases.<sup>6</sup>

**RISK FACTORS FOR BCG LYMPHADENITIS**

The BCG lymphadenitis occurs with a frequency that varies very widely depending on several vaccine and host related factors.<sup>1–7,13–15</sup> The vaccine related factors include:

- (1) The residual virulence of the BCG substrain. Some strains are more reactogenic than others.
- (2) The viability (the proportion of living and dead bacilli) of the final product.
- (3) Dose of the vaccine.

The host related factors include:

- (1) The age at vaccination. BCG vaccine given during the newborn period is associated with higher risk of lymphadenitis.

**B**acille Calmette-Guérin (BCG) vaccination has been used to prevent tuberculosis since 1921, and it was incorporated in the World Health Organisation's Expanded Programme on Immunisation in 1974 to strengthen the fight against childhood tuberculosis in developing countries.<sup>1</sup> Though there are controversies regarding its efficacy, it is generally agreed that the vaccine is effective against the disseminated disease and meningitis in childhood tuberculosis.<sup>2</sup>

BCG vaccine has a low incidence of serious adverse reactions, and is considered to be a safe vaccine.<sup>3,4</sup> BCG lymphadenitis, defined as the development of ipsilateral regional lymph node enlargement after BCG vaccination, is the most common complication resulting from this vaccination.<sup>2–4</sup> In its natural course, BCG lymphadenitis either undergoes spontaneous regression, or enlarges progressively and becomes suppurative. Several therapeutic interventions have been used or recommended for the treatment of BCG lymphadenitis without any definitive proof of their efficacy; as a result there are controversies regarding the most appropriate treatment of this condition.

**DEFINITION**

After intradermal injection, the BCG start multiplying rapidly at the site of inoculation and are later transported through the lymphatics to the

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**Box 1: Diagnosis of BCG lymphadenitis**

- Isolated axillary (or supraclavicular/cervical) lymph node enlargement.
- History of BCG vaccination on the same side.
- Absence of tenderness and raised temperature over the swelling.
- Absence of fever and other constitutional symptoms.
- Chest radiography, Mantoux reaction, and haematological analysis are not helpful. Fine needle aspiration cytology corroborates the clinical diagnosis in doubtful cases.

(2) The immunological responses to the vaccines. Serious immunodeficiency states like severe combined immunodeficiency and AIDS are associated with increased incidence of local as well as systemic disseminated BCG infection after vaccination.<sup>4 14 15</sup> The risk of BCG related complications appears to be increased even in patients with asymptomatic HIV infection, but the reactions are usually mild and the risk does not outweigh the benefits of BCG vaccination in children at high risk of tuberculosis.<sup>15</sup>

(3) Characteristics of the recipient population; these may also be important determinants of the risk.<sup>4</sup> This could account for the differences in the incidence of BCG lymphadenitis in different countries. The skill of the person giving the intradermal vaccination has been found to be a significant determinant of the risk,<sup>1-4 13</sup> although the role of faulty vaccine administration has been questioned.<sup>7</sup>

**NATURAL COURSE**

Two forms of BCG lymphadenitis can be recognised in its natural course.<sup>11 13</sup> The non-suppurative form, also called simple BCG lymphadenitis,<sup>3 13</sup> occurs in the beginning and frequently resolves spontaneously without any sequelae, within a period of few weeks.<sup>7 11</sup> In some cases, however, the affected lymph nodes may enlarge progressively and develop suppuration, marked by the appearance of fluctuations in the swelling with erythema and oedema of overlying skin.<sup>8 10 16</sup> Suppurative lymphadenitis can also develop abruptly within 2–4 months of BCG vaccination.<sup>8 13</sup> Once suppuration has supervened, the subsequent course is usually distinguished by the occurrence of spontaneous discharge and sinus formation. Healing eventually takes place through the cicatrization and closure of the sinus, but the whole process takes several months,<sup>7 11 16</sup> is unpleasant for the parents and the patient, and requires meticulous wound care. The resultant scar may have aesthetic implications.

Suppuration may develop in 30% to 80% of cases of BCG lymphadenitis.<sup>8-10</sup> Risk is higher if vaccine is given during the newborn period.<sup>6</sup> Rapidly developing BCG lymphadenitis appears more likely to suppurate.<sup>8 13</sup> The role of secondary infection by pyogenic bacteria in suppuration is not clear.<sup>5 6</sup>

**DIAGNOSIS**

The diagnosis of BCG lymphadenitis is clinical. The finding of isolated enlarged axillary (rarely supraclavicular or cervical) lymph nodes ipsilateral to the site of BCG vaccination, with no other identifiable cause for adenitis, is usually sufficient for making the diagnosis in the majority of cases.<sup>10 13 17</sup> Absence of fever, tenderness, and other constitutional symptoms differentiates it from pyogenic adenitis.<sup>11</sup> Differentiation from tuberculous lymphadenitis may be difficult, but cases of isolated axillary glandular tuberculosis are very rare.<sup>5</sup>

Investigations have a limited role in the diagnosis of BCG lymphadenitis, and are not routinely indicated. Haematological analysis, chest radiography, and the tuberculin test add little to the diagnosis. The cytopathology of the aspirate from the BCG lymphadenitis is not very different from that seen in

**Box 2: Management of BCG lymphadenitis****Medical**

- No role for antibiotics like erythromycin.
- Antituberculous drugs too are ineffective.
- Risk of adverse drug reactions.

**Needle aspiration**

- Recommended for suppurative BCG lymphadenitis.
- Prevents discharge and associated complications.
- Shortens the duration of healing.
- Safe.

**Surgical excision**

- Risk of general anaesthesia.
- Useful in cases with failed needle aspiration, multiloculated or matted lymph nodes, and draining sinuses.

tuberculous lymphadenitis.<sup>18</sup> Although microbiological confirmation is generally not required, finding of acid-fast bacilli in the smear or recovery of *Mycobacterium bovis* from the culture of aspirated material from the involved lymph nodes corroborates the diagnosis of BCG lymphadenitis.<sup>9 14 18</sup> Definitive identification of BCG that would require phase typing or gene analysis<sup>14 19</sup> and immune work-up are not usually needed unless disseminated BCG infection is suspected.<sup>11 14 15</sup> Isolation of pyogenic bacteria from the aspirate from suppurative BCG lymphadenitis has been reported, although the exact significance of this finding is not precisely known.<sup>5 6</sup>

**TREATMENT**

Treatment of BCG lymphadenitis has remained controversial. Since non-suppurative forms regress without any ill effects, and the suppurative form is associated with an unpleasant and prolonged course, prevention of suppuration becomes the most important objective in the treatment of BCG lymphadenitis. Once suppuration has occurred, the treatment should aim at promoting resolution and preventing spontaneous discharge and sinus formation.

**Medical management**

Drugs including antibiotics like oral erythromycin and antituberculous drugs like isoniazid and rifampicin have been used in the treatment of BCG lymphadenitis. Though uncontrolled observations suggested their efficacy,<sup>20 21</sup> results from controlled trials have indicated that these drugs neither reduce the risk of suppuration nor shorten the duration of healing.<sup>8 10 17 22</sup> This has further been corroborated in a recent meta-analysis.<sup>23</sup> Since non-suppurative BCG lymphadenitis is a benign condition, and drugs do not alter its course but can have adverse effects,<sup>8</sup> reassurance and expectant follow up is all that is required.<sup>8 9 11 22</sup>

**Needle aspiration**

Because suppurative BCG lymphadenitis is frequently complicated by spontaneous perforation with sinus formation, which may persist for several months, needle aspiration is recommended to prevent this complication and shorten the duration of healing.<sup>5 16 24</sup> Banani and Alborzi, in the only randomised controlled trial reported so far, demonstrated that needle aspiration(s) resulted in significantly higher (95% v 68%) and rapid (6.7 v 11.8 weeks) rates of healing of suppurative glands when compared with controls.<sup>24</sup> Usually one aspiration is effective, but repeated aspirations may be needed for some patients.<sup>16 24</sup> Some authors advocate intranodal injection of isoniazid aspiration after needle aspiration.<sup>17</sup>

**Surgical excision**

Though surgical excision is likely to be curative and will reduce the healing time, it requires general anaesthesia,<sup>12 16 25</sup>

### Questions (answers at end of paper)

1. What is the course of untreated non-suppurative lymphadenitis?
2. What is the outcome of suppurative BCG lymph nodes left untreated?
3. What is the role of medical treatment in the treatment of BCG lymphadenitis?
4. How best can one manage a case of BCG lymphadenitis?

which carries a risk to young children and infants. It is definitively not to be recommended for non-suppurative cases of BCG lymphadenitis. For suppurative cases, needle aspiration is considered a safer option.<sup>16,24</sup> Surgical excision may be needed when needle aspiration has failed as in the case of matted and multiloculated lymph nodes,<sup>24</sup> or when suppurative nodes have already drained with sinus formation.<sup>12,16</sup> The addition of antituberculous drugs after surgical excision<sup>7,25</sup> has not been found to be of any extra benefit.<sup>12</sup> Surgical incision is not recommended.<sup>9,16</sup>

### CONCLUSIONS

Non-suppurative BCG lymphadenitis is a benign condition and regresses spontaneously without any treatment. Antituberculous drugs are not effective. Suppurative lymph nodes are managed by needle aspiration to prevent sinus formation and to hasten the resolution. Surgical excision is only rarely required.

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### ANSWERS

1. Untreated non-suppurative lymphadenitis regresses spontaneously over a period of few weeks. In some cases, however, progressive enlargement and evolution into abscess formation can occur.
2. Though spontaneous regression can occur, the most likely outcome in these cases is the development of spontaneous perforation and sinus formation. Ultimate healing occurs by closure of the fistula through cicatrization, but the process usually takes several months.
3. Erythromycin and antituberculous drugs are ineffective in hastening regression or preventing suppuration in BCG lymphadenitis.
4. Non-suppurative BCG lymphadenitis is allowed to regress spontaneously. If suppuration develops, needle aspiration is done to prevent perforation and sinus formation. Surgical excision is resorted to if needle aspiration fails, as in cases with multiloculated or matted glands.