A Review of BCG Vaccine–Related Lymphadenitis and BCG-itis

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ABSTRACT: Tuberculosis (TB) is the leading infectious cause of death worldwide. BCG is the most widely used vaccine in the world. It prevents the most severe forms of TB meningitis and miliary TB disease. It is considered a safe vaccine, but it has been associated with local and systemic complications. Mild adverse events include local injection site reaction, while severe adverse events include osteomyelitis and osteitis, lymphadenitis and BCG-itis. Lymphadenitis is the most common complication associated with the vaccine and is characterized by ipsilateral lymph node enlargement. Lymphadenitis presents in a suppurative and nonsuppurative form. BCG-itis is the most serious complication of BCG vaccination, since it can cause death. Lymphadenitis and BCG-itis can be easily mistaken for other infections that are usually treated with antibiotic therapy; therefore, it is important to recognize them so as to initiate appropriate treatment, especially given increasing antibiotic resistance.

KEYWORDS: BCG-itis, bacille Calmette-Guérin (BCG), tuberculosis, lymphadenitis, tuberculosis scar

Tuberculosis (TB) is an infectious disease that requires a high index of suspicion, is difficult to treat, whose causative pathogen is prone to developing antibiotic resistance, and most importantly is the leading infectious cause of death worldwide.[1] Every year, more than 10 million people develop active TB disease, and almost 2 million die from it.[2]

The World Health Organization (WHO) developed an effective way of preventing TB by creating a vaccine. So far, the only WHO-approved vaccine is the BCG (bacille Calmette-Guérin) vaccine, which was introduced in 1921.[3] BCG is a cultured virulent *Mycobacterium bovis* strain that has been modified to lose its virulence potential so that it can be used as a vaccine. It was developed by attenuating an isolate from a cow with tubercular mastitis.[3,4] It is the most widely used vaccine in the world and is administered to approximately 100 million infants globally each year.[5] WHO recommends universal vaccination in countries with highly endemic TB or in settings with a high risk of TB exposure.[6] Neonatal vaccination with BCG is cost-effective in countries with either a medium or high incidence of TB compared with the cost of treating meningeal and miliary TB.[7-9]

The BCG vaccine prevents the most severe forms of TB, especially childhood TB meningitis and miliary TB disease, with an effectiveness rate of 80% against disseminated and meningeal TB and 50% against pulmonary TB; however, it does not prevent reactivation of latent TB infection, which is the main source of adult pulmonary disease.[5,6,8] BCG may offer protection against leprosy.[6] It has been associated with reduced childhood all-cause mortality and increased antibody response to other immunizations, such as changes in the immune response to malaria vaccination, making the vaccine not only effective against TB but also beneficial for other health conditions.[10] It has also been used in the treatment of superficial bladder carcinoma.[11]

Currently, 6 main strains account for more than 90% of the vaccines in use worldwide (Pasteur 1173 P2, Danish 1331, Glaxo 1077, Tokyo 172-1, Russian BCG-I, and Moreau RDJ strains), each with a different reactogenicity profile. Since there is no standardized production of the vaccine among manufacturers, the concentration of live particles in the vaccines ranges from 50,000 to 3 million per dose, and the incidence of adverse reactions varies among them. For example, the Russian and

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A BCG scar at the inoculation site of a young patient.

Gothenburg strains are known to induce more adverse reactions than the other strains.[3]

In general, BCG is considered a safe vaccine, but it has been associated with local and systemic complications.[12] It is important to know about and identify these adverse reactions so that they can be treated in a timely and appropriate manner. This review focuses mainly on BCG-itis and lymphadenitis reactions that can frequently be mistaken for nonmycobacterial infections, leading to inappropriate antibiotic use.

BCG ADVERSE EVENTS

Adverse reactions to the BCG vaccine are reported in 1% to 10% of administrations, but the true number of cases is likely to be underreported.[13,14] The most common events reported are suppurative lymphadenitis, keloid formation, and abscesses.[14] They may present from a few weeks up to 6 to 12 months after vaccine administration.[15]

WHO has classified the adverse events as mild or severe.[3] Mild adverse events include ulceration at the site of injection and adenopathies; severe adverse events can include osteitis or osteomyelitis and disseminated disease (BCG-itis), which usually occurs in immunocompromised patients.[16]

MILD ADVERSE EVENTS

A red, tender, and indurated papule usually is seen at the injection site.[3] This papule may appear 2 or more weeks after vaccination, it can progress to an ulcer, and then form a crust that falls off after approximately 6 weeks and leaves the commonly known BCG scar (**Figures 1 and 2**).[3,13] Another local reaction is swelling of the ipsilateral regional lymph nodes, most commonly in the axillary area but possibly also in the cervical and/or supraclavicular nodes. These tend to be less than 1.5 cm in diameter.[3] These swollen lymph nodes do not adhere to overlying skin and can be nonsuppurative or suppurative.[3,17] Treatment is not required for mild injection site reactions.[3] These reactions can occur despite correct intradermal administration of the vaccine.[3] Cutaneous lesions secondary to BCG vaccination are different from cutaneous TB.[17]

SEVERE ADVERSE EVENTS

Osteitis and osteomyelitis are among the rare consequences of BCG vaccination.[18,19] It is estimated that only 25% of BCG-associated cases of osteitis and osteomyelitis are diagnosed.[20] The conditions tend to appear 18 months after vaccination but can be seen up to 5 years later.[18,21] It is more common in the male population than in the female population.[20] BCG-induced osteitis and osteomyelitis affect the epiphysis and metaphysis of long bones due to these bones' wide vascularization, unlike TB osteomyelitis, which occurs more commonly in the spine and weight-bearing joints in older children and adults.[18,21] Usually, the presentation is unilateral.[18] Osteitis and osteomyelitis secondary to BCG vaccine show low response of inflammatory markers compared with the marked elevation of the erythrocyte sedimentation rate and C-reactive protein level that occurs in cases of osteomyelitis caused by other microorganisms.[18]

In 1971, Foucard and Hjelmstedt proposed 5 diagnostic criteria to facilitate the diagnosis of BCG-associated osteitis and osteomyelitis.[22] These criteria are: vaccination with BCG in the neonatal period, less than 4 years between the vaccination and symptom onset of, lack of contact between the child and any person with TB, a compatible clinical profile, and histopathology results suggestive of TB.[18,22] The diagnostic gold standard is the presence of a granulomatous reaction and caseous necrosis in a biopsy,[18] thus, requiring anti-TB treatment for 6 to 18 months.[18,21] Surgical treatment also has been recommended, since it allows physicians to obtain specimens for biopsy and facilitates the healing process.[21] Fortunately, BCG-associated osteitis and osteomyelitis have favorable outcomes.[20]

LYMPHADENITIS

BCG lymphadenitis is the most common complication associated with the BCG vaccine; it is characterized by ipsilateral regional lymph node enlargement.[23] BCG lymphadenitis generally undergoes spontaneous regression, but in some cases it becomes larger and suppurative.[24] For the BCG vaccination to be successful, a hematogenous dissemination of BCG must occur, known as normal BCG-itis. This process consists of

The same patient's BCG scar after spontaneously healing.

rapid multiplication of the bacilli at the site of inoculation after intradermal injection, then through the lymphatics to the regional lymph nodes.[23] Physicians should recognize that pathological reactions at the site of injection and slightly enlarged regional nodes after BCG vaccination are expected.[21] Subclinical lymphadenitis tends to regress spontaneously and most often goes unnoticed.[23]

Most cases of lymphadenitis appear within 6 months of vaccination, and almost all of them occur within 24 months. In more than 95% of cases, ipsilateral axillary nodes are involved; supraclavicular or cervical nodes may be occasionally enlarged in isolation or in association with axillary nodes. Most cases feature only 1 or 2 enlarged nodes.[23]

There are two forms of BCG lymphadenitis, suppurative and nonsuppurative, the latter of which represents most cases.[23,25] The nonsuppurative form is also called simple BCG lymphadenitis, which tends to resolve spontaneously within a period of weeks without any sequelae.[24]

The suppurative form is characterized by progressive enlargement of the affected lymph nodes with erythema, edema, and increased pigmentation of the overlying skin with pustule formation.[23,24] Suppuration occurs in 30% to 80% of cases of BCG lymphadenitis in a progressive way, or it can appear abruptly within 2 to 4 months after vaccination.[23] The more rapidly BCG lymphadenitis develops, the more likely it is to suppurate.[23] Following suppuration, there can be some discharge and sinus formation, which then closes and heals spontaneously. This process usually takes several months and requires frequent and meticulous wound care.[23,24] If it is left untreated, suppurative lymphadenitis can have a prolonged course of illness and leave unsightly scars, keloids, or both, but these adverse events are very uncommon.[24,25]

BCG lymphadenitis is a clinical diagnosis. Since most of the vaccination worldwide is done in the neonatal period, almost all cases of BCG lymphadenitis are diagnosed within the first 2 years of life.[23,24] An ipsilateral enlarged lymph node next to the BCG injection site with no other identifiable cause for adenitis is usually enough to make the diagnosis.[23] Cases of isolated axillary glandular tuberculosis are very rare.[24] Microbiological confirmation is not necessary, but isolating acid-fast bacilli (AFB) in the smear or recovery of *M bovis* should be done when disseminated BCG infection is suspected in patients who are immunocompromised.[23,24]

Treatment has remained controversial, since there is no consensus on the appropriate approach. The main objective is to prevent progression to suppuration, since this form of BCG lymphadenitis is associated with a prolonged course and more sequalae.[23] Three treatment options are available: antibiotic therapy, needle aspiration, and/or surgical excision.[24]

Medical treatment includes antibiotics such as erythromycin and anti-TB drugs such as isoniazid and rifampin.[23,24] These drugs cannot prevent progression of suppuration and do not shorten the duration of healing.[23,24,26] The only cases in which antibiotic treatment may be considered are those with superinfection with pyogenic bacteria such as *Staphylococcus aureus* or *Streptococcus pyogenes*.[24,26]

Needle aspiration is usually recommended in suppurative lymphadenitis to prevent the progression to sinus formation and to shorten the duration of healing, and it can also offer valuable diagnostic information (AFB smear, culture).[23,24] It also is a safer option than surgical excision, since it does not require general anesthesia, which can be risky for young infants.[26]

Surgical excision removes the affected lymph nodes and reduces the healing time.[23,24] This option should only be considered in children in whom repeated needle aspirations have failed or when suppurative nodes have caused sinus formations.[23,26]

BCG-ITIS

BCG-itis is the most serious complication of BCG vaccination.[26] It is an infection that affects several organ systems and has been found mainly in children with primary immunodeficiency, severe combined immunodeficiency, AIDS, and Mendelian susceptibility to mycobacterial disease, among other immune-system diseases; this is why, when presented with this entity, patients should be evaluated for immunodeficiency.[25,27,28] Other causes have been associated with this entity aside from immunocompromise, mainly related to the vaccine itself.[28]

BCG-itis an invasive infection characterized by involvement of at least 2 anatomic sites distant to the vaccination area, or compromise of the bloodstream or bone marrow, as well as isolation of the mycobacteria in culture.[28] The anatomic sites

must be of different organs systems; if BCG is present in the sputum and pleural fluid, it is considered as compromise of only one site.[28] Deaths secondary to disseminated BCG disease have been reported, primarily among immunocompromised patients.[25]

Clinical manifestations include fever, weight loss, anemia, generalized lymphadenopathies, hepatosplenomegaly, and rash.[27,28] In immunocompromised patients, the finding of a local or regional BCG infection should oblige a physician to look for BCG-itis.[28] Chest radiography, lung computed tomography scanning, and lumbar or gastric aspiration should be performed to evaluate for organ involvement.[28]

The diagnosis can be made by culture or molecular methods. Isolation of BCG is mandatory to make the diagnosis of BCG-itis.[28] The most reliable method is the identification of the RD1 deletion by polymerase chain reaction, which has a 100% sensitivity and specificity but it is highly expensive and not available in all countries.[28] Each BCG strain has a different susceptibility pattern, so treatment should be started according to the individual strain's susceptibility pattern.[26] *M bovis* is intrinsically resistant to pyrazinamide.[26] Treatment usually requires 4 medications; mycobacterial therapeutic regimens include isoniazid, rifampin, ethambutol, and streptomycin.[26]

CONCLUSION

BCG is the most administered vaccine worldwide and it is included in most developing countries' vaccination programs, since it is included in the global expanded program of immunization recommended by WHO. The frequency of adverse events tends to be very low, but it is important to know that they exist and how to treat them, since they can have serious implications in a child's quality of life. Lymphadenitis and BCG-itis are entities that can be easily mistaken for other infections that are usually treated with antibiotic therapy. Thus it is important to know how to recognize them so that appropriate treatment can be initiated, especially now that antibiotic resistance has been on the rise. BCG is a vaccine that has brought great worldwide benefits, especially by preventing the most severe forms of TB and by providing cross-immune reaction to other diseases. Its benefits generally outweigh its risks, and it should continue to be given in countries where TB is endemic until another vaccine can be developed that is more effective against pulmonary TB and that has fewer associated adverse effects. ■

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