

Bacille Calmette-Guérin Lymphadenitis and Immune Reconstitution Syndrome in HIV-infected Children on Antiretroviral Therapy in Jamaica

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ABSTRACT

The immune reconstitution inflammatory syndrome (IRIS) is a recognized complication associated with opportunistic infections occurring in HIV-infected individuals after the initiation of highly active antiretroviral therapy (HAART). We report on three HIV-infected infants with rapid progressor HIV disease who present with IRIS due to the BCG vaccine and occurring 3–6 weeks after initiation of HAART.

Linfadenitis por Calmette-Guérin y Síndrome de Reconstitución Inmune en Niños Infectados con el VIH Bajo Terapia Antiretroviral en Jamaica

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RESUMEN

El síndrome inflamatorio de la reconstitución inmune (SIRI) es una complicación reconocida asociada con infecciones oportunistas que ocurren en individuos infectados por el VIH, luego de su iniciación en la terapia antiretroviral altamente activa (TARAA). Se reporta el caso de tres infantes infectados por VIH con enfermedad VIH de progresión rápida, que se presentan con SIRI debido a la vacuna BCG, 3-6 semanas después de la iniciación de TARAA.

INTRODUCTION

The Bacille Calmette-Guérin (BCG) vaccine is a live vaccine derived from a strain of *Mycobacterium bovis* that was attenuated by Calmette and Guérin at the Pasteur Institute in Lille, France (1) and was first administered to humans in 1921. Several strains of the BCG vaccine are available worldwide and differ in their characteristics when grown in culture and in their ability to induce an immune response to tuberculin. Although there was a mass BCG vaccination campaign in Jamaica in the 1950s (2), this vaccine was only included in the Expanded Programme on Immunizations in

Jamaica in 1978.

Protective efficacy rates of the vaccine in young children vary from 52% to 100% for prevention of tuberculous meningitis and miliary tuberculosis (TB) and from 2% to 80% for prevention of pulmonary TB (3–7). Meta-analyses of BCG protective efficacy (8, 9) have confirmed that the vaccine efficacy for preventing serious forms of TB in children (meningitis and disseminated TB) is high (> 80%) but is significantly reduced in older children and adults.

Adverse effects are usually local reactions (ulceration or abscess formation) but infrequent and rarely serious or long-term complications may occur (10). These include ipsilateral axillary lymphadenitis, osteitis and disseminated BCG disease. Factors implicated in the pathogenesis of these reactions include the BCG dose, vaccine strain, method of vaccine administration and underlying immune deficiency. Outbreaks of BCG lymphadenitis and abscess formation have been previously described in immunocompetent children in Jamaica and St Lucia (11, 12).

There have been reports of BCG adenitis occurring in HIV-infected children since the beginning of the epidemic (13, 14). With increased access to antiretroviral therapy in less developed countries that administer BCG vaccine to neonates at birth, the phenomenon of immune reconstitution in-

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flammatory syndrome manifesting as BCG adenitis has been described (15, 16). The immune reconstitution inflammatory syndrome is an adverse manifestation of vigorous immune recovery that develops following initiation of highly active antiretroviral therapy (HAART). This inflammatory response is directed against a variety of opportunistic pathogens causing latent or subclinical infection, including mycobacterial organisms (17–21).

We report this case series of immune reconstitution inflammatory syndrome developing within a few weeks of the initiation of HAART in three BCG-vaccinated infants with rapid-progressor HIV/AIDS disease.

CASE SERIES

Case 1: A male infant born to HIV-positive parents received BCG vaccine at six weeks of age. He presented at age five months with respiratory tract infection, oral candidiasis, generalized wasting and regression of milestones. First-line HAART was commenced at age seven months with zidovudine, lamivudine and nevirapine. Three weeks later, he developed ulceration at the site of his BCG inoculation and an enlarged right axillary lymph node (5 x 4 cm) which increased to 10 x 6 cm and became fluctuant and hyperaemic (Figs. A and B). Concomitantly, the infant showed marked improvement in his nutritional, neurological and immunological status (Table). Nodal aspiration revealed purulent

material which stained positive for acid-fast bacilli (AFB) on Zeihl-Neelsen stain. Ongoing management comprised incision and drainage, daily dressings, oral and topical antibiotics for presumed secondary bacterial infection. The abscess and ulceration slowly resolved over a six-month period (Figs. C and D).

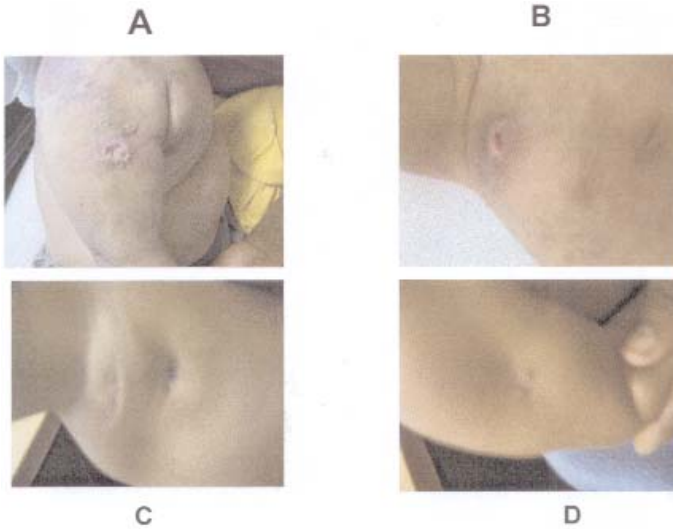
Case 2: A male infant whose mother was diagnosed HIV-positive during pregnancy presented at age five months with a history of not thriving, fever, oral thrush and respiratory tract infection. He had received BCG vaccine at birth. First-line HAART was commenced at seven months (zidovudine, lamivudine and nevirapine). Six weeks later, the BCG scar became ulcerated oozing purulent material and the ipsilateral axillary node was enlarged. Zeihl-Neelsen stain on the lymph node aspirate was positive for acid-fast bacilli. He was commenced on anti-tuberculous (anti-TB) therapy consisting of isoniazid, rifampicin, pyrazinamide and ethambutol. Clinical (weight), neurological and immunological improvement were observed (Table). At age 13 months, another right axillary swelling developed which revealed coagulase negative *Staphylococcus* and few acid-fast bacilli in the aspirate. He was treated with oral antibiotics and the lymphadenitis resolved after a seven-month period.

Case 3: A female infant born to a HIV-positive mother pre-

Table: Summaries of patients with BCG adenitis due to immune reconstitution inflammatory syndrome after initiation of HAART

Cases	Sex, Age at BCG vaccination	Clinical presentation	CDC category	Age at HAART initiation (months)	Weight (kg)		CD4 ⁺ (%/count) (cells/ μ L)		Interval to adenitis post-HAART (weeks)	Microbiology	Management	Outcome
					Baseline	6 months post HAART	Baseline	6 months post HAART				
1	M, 6 weeks	Wasting, respiratory tract infection, oral candidiasis, regression of milestones	C	7	6.46	10.20	40.0 / 228	40.7 / 1278	3	Acid-fast bacilli on ZN stain	Incision and drainage, oral and topical antibiotics, daily dressings	Slow resolution over 6 months
	M, At birth	Fever, oral candidiasis, respiratory tract infection, failure to thrive	C	7	4.00	6.94	16.0 / 177	43.7 / 1163	6	Acid-fast bacilli on ZN stain	Aspiration and quadruple anti-tuberculosis medication	Recurrence lymphadenitis at age 13 months resolution after 7 months
3	F, 2 days	Respiratory tract infection, wasting, generalized lymphadenopathy, oral and groin candidiasis	C	9	5.15	9.10	43.0 / 580	56.6 / 1698	4 (after regime switch)	Not done	Conservative management	Complete resolution after 4 months

NOTE. CDC – Centers for Disease Control and Prevention



Pictures of BCG scar ulceration and axillary adenitis following initiation of HAART in Case 1

- A. Ulceration at site of BCG scar (age 8 months); B. Abscess in ipsilateral axilla draining purulent material after incision; C. Healed BCG scar (age 13 months); D. Resolved lymphadenitis (age 13 months).

sented at age two months with respiratory tract infection, generalized lymphadenopathy, oral and groin candidiasis, generalized crusted scalp dermatitis and wasting. She received BCG vaccine on day 2 of life. First-line HAART was commenced at nine months (zidovudine, lamivudine and nevirapine). Two weeks later, she developed a Grade 3 adverse cutaneous reaction secondary to nevirapine which was switched to nelfinavir. At age 11 months, she developed zidovudine-induced anaemia resulting in a switch to stavudine. Four weeks later, a painful 3 x 4cm swelling developed in the right axilla. She was managed conservatively with oral antibiotics for presumed secondary infection but the adenitis resolved spontaneously after a four-month duration. She showed concomitant improvement in her clinical and immunological status (Table).

DISCUSSION

There have been few reports of immune reconstitution inflammatory syndrome (IRIS) associated with the BCG vaccine in HIV-infected children. The clinicopathological manifestations have included fever, ulceration and abscess formation at the BCG site, ipsilateral axillary lymphadenitis but no evidence of dissemination developing two to ten weeks after initiating highly active antiretroviral therapy (13–16, 22).

These cases in this report received BCG vaccine within six weeks of birth. On presentation to hospital had severe HIV disease. The development of ulceration and abscess formation at the BCG scar and axillary lymphadenitis occurred three to six weeks after initiation of HAART but was not accompanied by fever. Although plasma HIV-RNA assays

were unavailable, there was evidence of antiretroviral treatment efficacy based on the increased weight and immunological reconstitution for each infant. BCG disease was confined to the contiguous axillary lymph node and there was no evidence of dissemination. We were unable to obtain microbiological identification and susceptibility testing of the isolates due to limited laboratory capacity. But the response to management was consistent with the outcome in other reports (13–16, 22, 23).

Of note in Case 3, the BCG ulceration and axillary lymphadenopathy occurred after a second switch in antiretroviral therapy because of adverse effects. Without evidence from virologic assays, one presumes that treatment efficacy was optimally achieved with the third regime (stavudine, lamivudine and nelfinavir) resulting in immune reconstitution and onset of IRIS. We conclude that these cases represent IRIS due to the BCG vaccine in HIV-infected infants against evidence of concomitant immune reconstitution.

The definitive management of these children varied and there are no guidelines for the treatment of BCG adenitis due to IRIS. Management options in un-infected children range from conservative treatment (none), surgical drainage, administration of anti-TB drugs or a combination of drugs and surgery (10). A randomized placebo-controlled trial in immunocompetent Jamaican infants evaluated oral erythromycin and local isoniazid instillation therapy and demonstrated oral erythromycin to be more efficacious than placebo but less effective than intranodal isoniazid in the resolution of non-suppurative BCG lymphadenitis (24). Results from other controlled trials have revealed that drugs neither decreased the risk of suppuration nor shortened the duration of healing (25). For suppurative nodes, needle aspiration resulted in significantly higher and more rapid rates of healing than in the controls (26). The management of this complication remains controversial and the treatment option is likely to be dependent on the clinical state of the child and the assessment of the attending physician. The World Health Organization (WHO) suggests drainage and direct instillation of an anti-TB drug into the lesion for adherent or fistulated lymph nodes. Non-adherent lesions tend to heal spontaneously without treatment (9, 10, 23). Surgical excision, though probably curative carries risks associated with general anaesthesia and should be confined to cases of failed needle aspiration *eg* matted or multiloculated nodes or suppurative nodes with sinus formation (25, 26).

Suggestions have been made to change the policy regarding BCG vaccination because of increased risk for disseminated BCG disease among HIV-infected children (14, 22, 27) and the occurrence of IRIS. In addition, the proven efficacy of BCG vaccine in HIV-infected populations has not been evaluated.

In a recent policy review by the WHO Global Advisory Committee on Vaccine Safety on the use of BCG vaccination for children infected with HIV (28), data from retrospective

studies indicated a higher risk of disseminated BCG disease developing in children infected with HIV who were vaccinated at birth and who later developed AIDS. The reported risk associated with vaccinating HIV-infected children may outweigh the benefits of preventing severe tuberculosis, especially since the protective effect of BCG against tuberculosis in HIV-infected children has not been validated. The committee concluded that the BCG vaccine should not be used in children with symptomatic HIV infection.

WHO still currently recommends administration of a single dose of BCG vaccine to all infants living in areas where tuberculosis is highly endemic and to infants and children at particular risk of exposure to tuberculosis in low endemic countries. The BCG vaccine is contraindicated in children with symptomatic HIV infection and other immune impaired circumstances. The challenge for many resource-limited settings is limited diagnostic capacity for early identification (< 6 weeks of age) of infants infected with HIV at birth. Hence, in such settings, the BCG vaccination administration should be continued at birth to all infants regardless of HIV exposure but with very close follow-up of HIV-exposed infants until their HIV infection status has been definitively clarified.

In Jamaica, against the background of mycobacteriosis and the recent resurgence of childhood tuberculosis infection associated with the HIV epidemic (29, 30), the benefit of BCG vaccination may outweigh the possible risks. The Ministry of Health, Jamaica, endorses the current policy of the WHO to vaccinate all newborns with BCG within six weeks of life, regardless of perinatal exposure to HIV (31). Close follow-up of HIV-exposed infants is recommended and virologic testing (RNA PCR) should be done at six weeks and three months of age to clarify the infant's serological status.

In conclusion, the BCG vaccine is safe and has a high protective effect for serious tuberculous disease in young infants, although this has not been validated in HIV-infected populations. The phenomenon of IRIS can occur due to the *M bovis* strain vaccine in HIV-infected infants who initiate HAART but this must be distinguished from uncommon serious BCG disease (disseminated). The optimal management of IRIS BCG disease is unclear but the outcome is usually favourable. Healthcare practitioners should continue to administer the BCG vaccine to infants within six weeks of life regardless of perinatal exposure to HIV.

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