ORIGINAL ARTICLE

Observational case series of Immune Reconstitution Inflammatory Syndrome (IRIS) following initiation of Antiretroviral Therapy in infants with absent BCG scars in Lusaka, Zambia

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ABSTRACT

Reported here is the case series of six infants presenting with immune reconstitution syndrome following the initiation of antiretroviral therapy (ARV). The infants had no BCG scars at the time of starting ARVs and the mean duration of appearance of the cold abscess / lymphadenitis on the ipsilateral side of the BCG site was 2 – 8 weeks. Mycobacterial speciation studies of the fine needle aspirate material showed *Mycobacterium Bovis,* BCG strain. Two of the patients had to require antimycobacterial therapy.

INTRODUCTION

In Zambia, Bacille Calmette-Guerin (BCG), a live attenuated *Mycobacterium bovis* strain vaccine, is universally given to neonates at birth or shortly thereafter in conformity with the recommendations of the World Health Organisation[1]. BCG vaccine is given to this population of neonates regardless of their HIV status as they are asymptomatic in the early neonatal period[1]. The vaccine coverage rate for BCG currently stands at 95%[2].

Antiretroviral (ARVs) therapy has been available in selected public health service in Zambia since 2003 and over the years this has been scaled up to nearly every health centre[3]. The ARVs are free and are principally supplied by the donor community like PEPFAR, Clinton Foundation, Global Funds and to some extent the Zambian Government[3]. Of the estimated 76,000 children infected with HIV in 2010, there are currently well over 23,000 children on ARVs of the 34,000 who require treatment in Zambia[3].

Voluntary Counseling and Testing (VCT) in pregnancy is the cornerstone of Prevention of Mother to Child Transmission (PMTCT) of HIV and in the urban setting in Zambia acceptability is currently put at 70% and is lower in the rural population[4].

ETHODS

Site setting: The study was done in one of the 5 general paediatric units at The University Teaching Hospital, Lusaka and the admission rota is 1:5. The units manage the patients they admit during their emergency admission days and inpatients with further follow-ups in review clinics

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HIV Counselors: Nurse counselors stationed in the admission ward offer VCT to all parents/guardians whose children are admitted to the admission ward. Unless they are discharged before VCT, those transferred to the wards as in-pateints who were missed in admission ward are offered VCT.

Patients: Dot Blood Sample (DBS) is taken on filter paper for HIV I/II DNA PCR by the nurse counselors from neonates and young children before 18 months of age who are found to be positive on Rapid HIV I/II screening tests (Determine HIV-1/2, Inverness Medical Japan Co., Ltd and Uni-Gold™ , Trinity Biotech Plc, Ireland). Further tests like CD4, FBC, Liver and renal function tests are done on those with detected HIV DNA on polymerase chain reaction (PCR).

Anti-Retroviral Therapy (ART): Infants initiated on ART on the ward or follow up clinics are reviewed fortnightly in the first month in out-patient clinic run by the unit. Those infants who were found to have BGC reactivation which was defined as swelling or ulceration at the BCG site and or ipsilateral axillary lymphadenopathy or ulceration are the subjects of this observational case series study.

Needle aspirates from BCG site swelling and or ipsilateral axillary lymphnodes. Thin needle aspirate technique was used to aspirate BCG cold abscesses and axillary lymphnodes. The aspirates were taken into a plain bottle and transported to the TB Molecular laboratory within an hour.

RESULTS

Five infants were identified in the unit during a period of two years. Table 1 shows the clinical characteristics of the infants. All the children who presented with BCG adenitis were young infants except one who was aged 7 months. Clinically at time of first presentation to hospital, the infants were very ill presenting with severe pneumonia and had no BCG scars (Table 1)

Table 1: *Clinical profile of young infants with IRIS due to BCG*

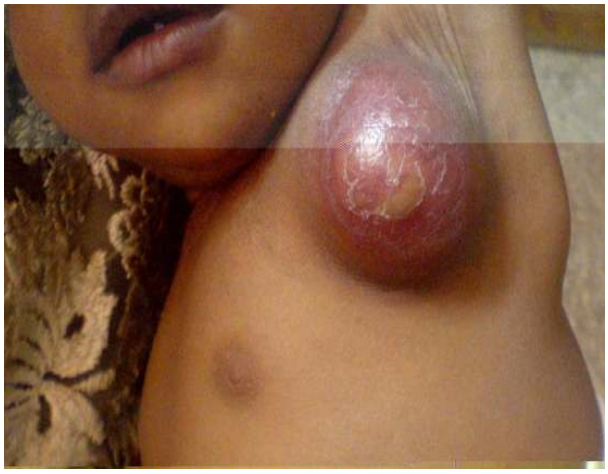
Characteristic	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
1. Clinical profile prior to initiation of ART						
- Age (months)	2	1	3	3	7	7
- Sex	M	M	M	F	M	M
- BCG scar	Absent	Absent	Absent	Absent	Absent	Absent
- Admission diagnosis	Pneumonia ?PCP	Septicaemia with FTT	Pneumonia	Septicaemia, Diarrhoea with FTT	Atypical Pneumonia, ?PCP	Septicaemia, Meningitis
2. Laboratory profile						
- DBS – PCR	Detected	Detected	Detected	Detected	Detected	Detected
- CD4	572(14.7%)	524(20.0%)	364(30.9%)	159(15.0%)	336(7%)	282(10.0%)
- Hb(g/dl)	11.6	12.3	9.2g	10.8	10.2	9.9
- WBC (x 10^9 /L)	11.2	7.2	5.9	3.5	9.2	6.3
Lymphoctes	3.9 (35.0%)	2.6(33.6%)	2.8(48.9%)	30.7%	47.9%	44.1%
Monocytes	1.0 (9.8%)		0.4(7.8%)	12.3%	12%	9.5%
Neutrophiles	6.3(54.5%)	1.5(18.8%)	2.5(43.3%)	50.1%	39.2%	46.4%
Liver/Renal						
- *AST* (U/L)	13	15	119	36.5	46.3	157
- *ALT* (U/L)	66	24	271	112.6	12.2	96
- *Creatinine µmol/L*	35	17	-----	43.5	38.8	32
ART & BCG IRIS details						
3. ART initiation	AZT/3TC/NVP	d4T/3TC/NVP	d4T/3TC/NVP	AZT/3TC/NVP	d4T/3TC/NVP	d4T/3TC/NVP
4. Time of appearance of left axillary lymphadenitis after ART initiation	2 weeks	4 weeks	4 weeks	8 weeks	8 weeks	3 weeks
5. Management of BCG cold abscess (IRIS)	Continued ARVs	Continued ARVs	ATT started and continued ARVs. NVP replaced with ABC	Continued ARVs	ATT started and continued ARVs. Replaced NVP with ABC	ATT started and continued ARVs. NVP replaced with ABC

ABC – Abacavir, AZT – Zidovudine, d4T – Stavudine, NVP – Niverapine

HIV DNA was detected on DBS of all the five infants (Table 1). Their CD4 profiles showed that they were severely immunocompromised, CD4 less than 20%, except for Case no. 3 who had a CD4 count of 30.9%. Of note on the full blood count was a marked monocytosis.

Swellings at the BCG site and ipsilateral axillary lymphadenitis appeared 2 – 8 weeks after initiation of ARVs. Of note is that the mothers had infact noted the swellings much earlier and the upper limit of 8 weeks is the time that the mothers became concerned and came on an unscheduled clinic visit. In mycobacterium speciation analysis, mycobacterium bovis, BCG strain was identified (Figure 1) than the wild mycobacterium tuberculosis species. Figure 2 shows a typical ipsilateral left axillary cold abscess as BCG injection site in young infant.

Figure 2: *Typical Ipsilateral Left Axillary Cold Abscess as BCG injection site in young infant.*



DISCUSSION

This observational case series report describes the risk of BCG vaccine causing axillary BCG lymphadenitis and cold abscesses in HIV vertically infected young infants initiated on ARVs. Speciation studies showed that these infants were infected with mycobacterium bovis, BCG strain (Figure 1). All the young infants seen did not have a BCG scar at the time of initiation of ARVs implying that they failed to mount a delayed type hypersensitivity reaction to BCG vaccine due to immune-suppression. In vivo studies have previously conclusively shown that short course ARVs restored mycobacterium- specific T cell immunity in Macaque models co-infected with simian immunodeficiency virus and BCG (5). Therefore, lymphadenitis and cold abscesses in these young infants developed as a result of the restoration of immunity. Anecdotally, some young infants who fail to develop BCG vaccine scar after 6 to 8 weeks of receiving a vaccine go on to receive a second dose and this practice which is widespread in Zambia should be discouraged.

Studies elsewhere have consistently brought the safety of the current live attenuated BCG vaccines in HIV endemic areas under question. As ARVs become more widespread in Zambia, and indeed in sub-Saharan Africa, more young infants who are HIV vertically infected are likely to be at risk of BCG lymphadenitis and cold abscesses. This can disseminate in BCG disease with fatal outcome. Some studies have described disseminated BCG disease in HIV infected infants[6,7,8].

Some BCG strains, like the Danish strain have been shown to be inherently resistant to isoniazide and acquire resistance to rifampicin during therapy has been demonstrated in HIV infected infants with BCG disease[9]. This has far reaching consequencies in the management of infants with BCG lymphadenothay / cold abscesses who may progress to BCG disease. Case no. 3 and 5 received anti-mycobacterial therapy (pyrazinamide, isoniazide, and rifampicin). On follow up, the patients responded well to treatment. In poor resource settings like Zambia, it may not be possible to diagnose BCG resistant strains to isoniazide or rifampicin particularly in those infants presenting outside the University Teaching Hospital in Lusaka where facilities for such diagnosis are not available.

Even in the face of increasing PMTCT coverage in Zambia, a new BCG vaccine to protect young infants from serious forms of tuberculosis like tuberculous meningitis and miliary tuberculosis is warranted. Furthermore, there is urgent need to replace the current live attenuated BCG vaccines with other vaccines such as recombinant BCG vaccines[10,11].

The current BCG vaccine given at birth or in early neonatal period is causing more harm than good particularly in remote rural settings where HIV infected infants are commenced on ARVs. These settings have no access to diagnostic facilities. The authors have attended to young infants with unresolving pneumonias and pyrexia of unknown origin which have empirically resolved on ATT. The only risk factor in most of these young infants has been BCG vaccine and lack of a BCG scar. The authors recommend that young infants being commenced on ART, should receive a standard course of ATT for the first 6 - 8 weeks. The benefits of this approach will be the prevention of IRIS due to BCG vaccine as BCG disease remains undiagnosed though diagnosis of BCG vaccine site abscess / ulceration and BCG adenitis in the ipsilateral axillar is obvious.

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