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Case Report

Immune reconstitution inflammatory syndrome: Case series from Abuja

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There is paucity of information on immune reconstitution inflammatory syndrome in children in Nigeria. We reported two cases of IRIS in a 7 and 14 years HIV infected Nigerian boys managed at the University of Abuja Teaching Hospital, Gwagwalada, Nigeria. Immune reconstitution inflammatory syndrome was diagnosed and managed in 4 out of 1,027 (0.38%) HIV positive paediatric patients started on antiretroviral therapy at the health institution over a 6 years period.

Keywords: Immune reconstitution inflammatory syndrome, highly active antiretroviral therapy, Nigeria.

INTRODUCTION

The advent of antiretroviral therapy (ART) has dramatically changed the prognosis of HIV disease by enabling sustained suppression of HIV replication and recovery of CD4 cells (Lederman et al., 2001). Within the first few months of ART, the HIV viral load sharply decreases, whereas the number of CD4 cells rapidly increases (Lederman et al., 2001). This leads to an increased capacity to mount inflammatory reactions against both infectious and noninfectious antigens. Immune reconstitution inflammatory syndrome (IRIS) which is defined as unexpected and paradoxical clinical deterioration immediately after initiation of ART in HIV positive patients, is an inflammatory reaction from improvement in the immune system interaction to specific infectious and non-infectious antigen (Hirsch et al., (2004). This inflammatory reaction is directed against pathogens causing latent or subclinical infection. In the infectious category, most frequently reported cases are *Mycobacterium tuberculosis* (MTB), *Cryptococcal meningitis, Varicella zoster, Herpes viruses, Cytomegalovirus* (CMV*), Pneumocytis (carinii) jiroveci pneumonia* (PCP), *Hepatitis B and C* (Murdoch et al., 2007). Other conditions are *Mycobacterium avium complex* (MAC), latent cryptococcal infections, etc. Besides a direct reaction to infectious and non infectious agents, a third group of patients react as a result of their host genetic susceptibility. IRIS associated with infectious agents may arise in two settings: unmasking the disease in a clinically stable patient with previously unrecognized infection (unmasking), or worsening of disease in a patient being treated for on-going opportunistic infection (worsening type), (Narita et al., 1998). There have been several reports of IRIS in HIV infected children from Thailand, South Africa, and India (Sirisanthana et al., 2004; Mohanty, 2010; Rabie, 2009). Very few cases have so far been reported in children in this environment hence the present case presentations.

CASE REPORT 1

JD is a 7 year old HIV infected male patient, the main complaint at the time of first presentation in our health care facility was progressive weight loss, lethargy and chest pain. Examination revealed an ill-looking boy, wasted (weight 15 kg < 5th percentile of National Centre for Health Statistic [NCHS] international growth chart), he was found to be mildly pale, lethargic, having generalized significant peripheral lymphadenopathy (measuring 2.5x 2.5cm, multiple, discrete, mobile and non tender). He also had whitish plaque on the buccal mucosa, patchy roundish scaly lesions on the head (tinea coporis), and tender hepato-splenomegaly of 5cm and 3cm. Total white blood cell count (TWBC) was 2.1x109/uL, with neutrophil of 74.2% and lymphocyte of 20.3%, platelet was adequate, while electrolyte sedimentation rate (ESR) was 60mm/hr, and haemoglobin level (6.7g/dL). CD4 cell count/ percentage was 32cells /ul /3.4% at initial visit.

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Electrolytes /urea, creatinine, liver function test (LFT), cholesterol, blood sugar were all within normal limit, and no abnormality was also seen on chest radiograph. He was commenced on antiretroviral therapy (ART): stavudine (D4T), lamivudine (3TC), and nevirapine (NVP), after 3 consecutive adherence counseling on the importance and dangers of not adhering to ART. Co-trimoxazol (CTZ), nystatin oral suspension, cotrimazol cream, haematinics, multi-vitamins, and high protein/ calorie dense food (action meal, a nutrient supplement for HIV positive older children and adults) were all started. Two weeks after the commencement of ART, patient came back to the clinic with 7 days history of cough, 3 days history of high grade fever, loss of appetite, body weakness/ body pains, and a day history of vomiting and diarrhoea. Examination at the second presentation revealed a more ill looking boy, grossly wasted (weight had decreased from 15 kg to 13 kg), lethargic, now febrile with a temperature of 39.5^{O}C, the generalized lymphadenopathy had increased in size from 2.5 x 2.5 cm to 3.5 x 3.5 cm and now tender. He was also found to be in respiratory distress (respiratory rate [RR] of 42 breaths per minute) with dull percussion note and decreased breath sound on the right lower lung field posteriorly. Hepatomegaly has increased from 5cm to 7cm, splenomagaly also from 3 cm to 4cm, and there was minimal ascites. Repeat TWBC was 3.8x109/uL, with neutrophil of 59.4% and lymphocyte of 38.2%, platelet was adequate, ESR has also increased from 60mm/hr to 135mm/hr and haemoglobin level dropped from 6.7g/dL to 3.8g/dL. Chest showed bilateral peri-hilar and right middle/ lower zone opacity, blood/ stool cultures were negative, and no malaria parasite was seen in both the thin and thick blood smear. Repeat CD4 cell count/percentage was 65 cells/ul and percentage of 6.3%. Patient was however commenced on parenteral antibiotic (augumentin and genticin), treated for malaria with artesunate and amodiaquine tablets, and received blood transfusion. Augumentin was latter changed to ceftraxione when there was no improvement in the clinical condition. Fever had persisted with no isolate on the blood culture, and no malaria parasite on blood smear, Mantoux test showed area of induration of < 8mm in diameter, and sputum for acid fast bacilli (AFB) was negative 3x.There was evidence of matted bowel loops in a mesh of lower level intra-peritoneal echo suggestive of exudation in abdominal ultra sonography. In the absence of culture facilities for *Mycobacterium tuberculosis* (TB), therapeutic trail of anti-TB drugs were commenced: rifampicin, isoniazide, pyrazinamide and streptomycin were added to the management, and patient continued on high calorie/ protein nutrient supplement. Patient received 2 blood transfusions, and NVP changed to efavirenz (EFV). Possibility of unmasking type of IRIS was entertained when there was no improvement in the clinical condition of the patient with above management. Steroid was introduced and patient did well after 2 weeks on predisolone, temperature settled, respiratory rate became normal, positive chest findings regressed, and patient became ambulatory, started gaining weight and was discharged home after one month on admission. He is presently doing well on out-patient.

CASE REPORT 2

We report a case of a 14 year old boy (BR), a referral from neighbouring primary health centre with a 2 year history of recurrent diarrhoea, cough of 4 months duration, progressive weight loss, drenching night sweats and abdominal pains all of 2 months. The mother died 4 months ago from HIV/TB co-infection, and was not on anti-TB or ART before her death. Father and one other younger sib were positive for HIV infection and yet to commenced ART. Physical examination showed a chronically ill looking boy, severely wasted (weight of 19 kg < 5th percentile of NCHS growth chart), he was conscious, lethargic, moderately pale, had significant generalized lymphadenopathy (measuring 2.5cm by 2.5cm, discrete, mobile and non tender), and hyperpigmented lesions all over the body. Respiratory rate was 38 breaths per minute, with dull percussion note and crepitations on the right middle/ lower lung zone anteriorly and posteriorly. Abdomen was scaphoid, with mild generalized tenderness; liver and spleen were enlarged by 6cm and 4 cm respectively. HIV test was positive, CD4cell count and percentage were 12cells/uL and 1.9% respectively. TWBC was 2.4x109/uL, with neutrophil of 62% and lymphocyte of 26.3%, platelet was adequate, ESR was 150mm/hr, and packed cell volume (PCV) was 27%. Urea and electrolytes were within normal limit,, creatinine and liver function test were also normal. Chest x-ray showed increased peri-hilar markings with opacity at the right lower lung field, mantoux had 10mm diameter indurations, and sputum microscopy for acid fast bacilli (AFB) x3 was negative, (no culture facility was available for AFB). Stool culture grew E.coli and staphlococcus aureus both sensitive to ciporofloxacin and genticin. He received 10 days course of the ciprofloxacin and genticin, commenced on anti-TB therapy (rifampicin, isoniazide, pyrazinamide and streptomycin), and high calorie and protein diet. After 2weeks on anti-TB therapy, ARV was introduced to his treatment: D4T, 3TC and EFV. Patient subsequently developed high grade persistent fever (40^{O}C), severe respiratory distress, and chest pain 10 days after starting ART. He was found to be very ill, severely pale, RR was 46 breaths/min, pulse rate of 140 beat/ minute, and PCV of 12%. He received blood transfusion, treated for malaria with artesunate and amodioquine, had antibiotics (ceftriaxone for 7 days), continued on HAART and anti-TB, and high protein/ calorie diet. Condition continued deteriorating inspite of the above management, and possibility of worsening type of IRIS was entertained and steroid was added to

management. Patient condition also improved subsequently, and was latter discharged home. Present weight and CD4 cell count at 6 months of complete anti TB was 26.8 kg (10th percentile of NCHS international growth chart) and 464cells/uL and percentage of 21.3% respectively.

DISCUSSION

IRIS on initiation of highly active anti-retroviral therapy (HAART) is rare in this environment. Only 4 cases among 1,027 (0.38%) HIV infected children commenced on ART in our health institution developed this condition over a 6 years period. This was in contrast to studies from other developing countries where incidence of IRIS associated especially with TB was seen in 11- 43% of cases; in South Africa a reported incidence of 21% was documented (Rabie, 2009), in India 8% (Mohanty, 2010), and Thailand 25.3% (Sirisanthana et al., 2004 ; Puthanakit et al., 2006b). IRIS is commonly associated with *Mycobacterium* infections in greater than 50% of cases, (Narita et al., 1998; Sirisanthana et al., 2004; Rabie, 2009). and it is said to be high in areas of high TB prevalence (British HIV Association guidelines on TB/HIV infection, 2005 ; Puthanakit et al , 2006b). Despite many reported cases of TB-HIV co- infection in children in this environment (10 -20%) (Okechukwu et al., 2008; Ugochukwu, 2006), only few case reports on IRIS is available in children in this country. Factors contributing to low cases of IRIS in our environment could be as a result of under- reporting of cases and low-availability of HAART to HIV paediatric patients countrywide. Only 5% coverage of HAART to HIV infected children has been achieved in the country as of 2009 {Federal Ministry of Health Nigeria, National guidelines for paediatric HIV and AIDS, 2009). The inability of health personnel to suspect it in the midst of poor laboratory back-up or, ascribe the unfolding scenario to a different clinical interpretation may as well have contributed to the probable low documentation. The incidence of IRIS is however expected to increase with scale up of ART to more infected children in the country and clinicians should be on the watch out for it.

IRIS in HIV patients is usually seen in severely immune depleted patients with very low CD4 cell cell count. It is also possible that the lower the CD4 count, the more severe IRIS is expected. The two cases reported in this case series presented with very low CD4 cell count / percentage (32 cell/uL and 3.4% for case 1, and 12 cells/ul and 1.9% for case 2). Other workers (Sirisanthana et al., 2004; Mohanty, 2010; British HIV Association (BHIVA) guidelines on TB/HIV infection, 2005 ; Puthanakit et al., 2006b; Puthanakit et al., 2006a), have also reported very low CD4 cell count among their study cohorts. Although the exact pathogenesis of IRIS is not known, it has been found that the successful response to HAART produces pro-inflammatory cytokines or an immune deregulation in the absence of regulatory cytokines, this has resulted in a robust immune system (Sirisanthana et al., 2004; Mohanty, 2010). The predominant host defense against extracellular pathogens is T helper (TH)1 cells. HIV infection is known to infect and deplete CD4 T-cells including T regulatory (T-regs) cells. Following initiation of HAART, a rapid recovery of pathogen-specific TH1 cells has been reported, including those directed at intercurrent infections, and reconstitution of T-regs appeared to be much slower (Boulware et al., 2008). In this situation of imbalance, an IRIS event could be attributed to an exaggerated, uncontrolled inflammatory immune response of TH1 cells in the absence or deficiency of the normal physiological T-cell regulatory control mechanisms (Boulware et al., 2008). This exaggerated inflammatory process could be triggered by even low frequencies of reconstituted antigen-specific TH1 cells following ART initiation.

There are two clinical types of IRIS in this two case report: the unmasking and worsening type, both started within the first two weeks of commencing HAART. This appeared similar with what was reported by (Sirisanthana et al., 2004; Puthanakit et al., 2006a), and (Narita et al., 1998), both noted a median onset of within 12-21 days of initiation of ART. The main clinical presentations in these case series include high fever, increasing lymphadenopathy, respiratory symptoms, new pulmonary infiltrates, non-specific abdominal/chest pains, diarrheoa, vomiting, ascites and anaemia. These symptoms were not different from what has been reported elsewhere in both adults and children (Sirisanthana et al., 2004; Mohanty, 2010; Rabie, 2009; British HIV Association guidelines on TB/HIV infection, 2005; Puthanakit et al., 2006b ; Puthanakit et al., 2006a; Boulware et al., 2008; Philip et al., 2005). Surprisingly, many reported cases of IRIS have not documented severe weight loss among their study subjects (Sirisanthana et al., 2004; Rabie, 2009; Puthanakit et al., 2006b; Puthanakit et al., 2006a). Apart from very low CD4 cell count at presentation, the two patients, and even the two unreported ones presented with severe weight loss. Whether severe weight loss could be used to identify those at risk of IRIS especially in resource limited setting with limited diagnostic facilities need to be further evaluated.

CONCLUSION

The prevalence of IRIS in HIV-infected children after initiation of HAART is very low in this environment. Clinicians should have high index of suspicion in the first few weeks of commencing HAART especially in those with very low CD4cell count, and severe weight loss.

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