Nigerian Journal of Paediatrics 2007; 34 (1&2): 43-47

Suspected Multidrug Resistant Tuberculosis: a Case Report

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Abstract

Abdulkarim AA, Saka AO, Oloko G, Durowaye M. Suspected Multidrug Resistant Tuberculosis: a Case Report. *Nigerian Journal of Paediatrics* 2007; 34: 43. Tuberculosis (TB) remains a disease of clinical and public health importance globally with over nine million cases occurring yearly. An increasing number of cases has been identified all over the world in the past two decades because of the Human Immunodeficiency Virus pandemic. The emergence of mutated drug resistant and multidrug resistant strains offers new challenges to the clinician as well as the public health physician. The present case report draws attention to the problem of multidrug resistant TB and the implications for TB control if not adequately tackled.

Key words: Multidrug resistant; Tuberculosis; challenge.

Introduction

TUBERCULOSIS (TB) is one of the oldest diseases known to man and is caused mainly by *Mycobacterium tuberculosis*. Despite the age long relationship, the disease remains a global emergency today. In the last two decades, there have been increasing number of cases of Tb all over the world particularly in Africa and Asia. The TB crisis is being fuelled by the Human Immunodeficiency Virus (HIV)/Acquired Immune Deficiency Syndrome (AIDS) pandemic and the emergence and propagation of multidrug resistance (MDR). It has been estimated that TB would cause 30 million deaths before 2015.[1-3] In Nigeria, the problem of TB is further compounded by the low routine immunization coverage.

Multidrug resistance (MDR) strains of the organism are increasingly being identified all over the world with Africa and Eastern Europe having the highest rates.[4] So also is the issue of amplification of resistance- the sequential development of resistance to each drug in a treatment regimen. Lack of compliance and the use of already weakened drug regimen facilitate development of resistance. The fact that drug susceptibility testing (DST) is not a feature of the DOTS (Directly Observed Treatment Short course) strategy used in global TB control programme means that continuing transmission of resistant and at times, MDR strains is undetected. This may actually result in higher transmission rates with increase in mortality.[5,6] Even in tertiary centres in Nigeria, DST is not done routinely. This case report of a suspected MDR-TB is therefore presented to draw attention to the challenges in the management of patients with TB and a diagnosis of MDR in our setting.

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Case Report

SY, a 13-year-old boy, presented at the Emergency Paediatric Unit of the University of Ilorin Teaching Hospital with bone pains, neck swellings and fever of two months' duration. He experienced sharp non-radiating pains in both lower limbs which had gradually increased in severity. There was no associated limitation in movement until a few days before admission. At the same time, multiple bilateral neck swellings which were not painful but had gradually been increasing in size were noticed by the child and his mother. There was no history of associated sore throat or difficulty in breathing or swallowing. He experienced a low grade fever for the same duration of time as the neck swellings but there was no excessive night sweating. Two weeks prior to presentation and admission to the hospital, bilateral painful eye protrusion was noticed and this had been increasing in size, although at a slow rate since then. He developed a sudden loss of vision in the left eye one week prior to presentation, and one

day before admission, he had an episode of generalized tonic-clonic seizure which lasted for about five minutes. At the time of initial examination, a similar seizure was observed and was aborted with five ml of intramuscular paraldehyde. No loss of consciousness followed the convulsion.

There was a positive history of weight loss that had been slowly progressive and a history of recurrent bilateral nose bleeds. There was no history of pain in the upper limbs, swellings in the limbs, trauma or history suggestive of sickle cell anaemia in the patient or family members. He had received BCG in the first week of life. There was no history of cough or contact with a known person with undue weight loss or chronic cough, neither had he had bleeding from the gum or other sites. There had been no loosening or recent loss of teeth, and he had not engaged in sexual activity of any form; there was no other significant history of note. He had been treated at a private hospital with several injections and tablets but no history to suggest previous anti-tuberculous drug use.

Essential findings on general physical examination included lethargy, moderate pallor, fever with a temperature of 38.5æ%C, cervical and submental discrete and significant lymph node enlargement measuring 2x2 cm, and petechiae on the lower limbs. Respiratory examination revealed reduced breath sounds over the right lower zones. Cardiovascular findings on admission were normal. Mild abdominal distension was noted and both liver and spleen were palpable to three cm below the respective costal margins while abdominal percussion note was tympanitic. Eye examination showed that the left anterior chamber was shallow with prolapsed uveal tissue but the optic disc was pink. Central nervous system findings were normal except for lethargy.

Table I

Results of Investigations

Full blood count	
White cell count (WBC)	Total $20x10^9$/L, neutrophils 90%, lymphocytes 8%, eosinophils 2%
Packed cell volume	31%
Platelet count	$924x10^9$/L
Blast cells	Absent
Erythrocyte sedimentation rate (ESR)	
On admission	84mm/hour (hr)
2 weeks later	75mm/hr
4 weeks later	48mm/hr
6 weeks later	58mm/hr
10 weeks later	25mm/hr
Haemoglobin genotype	AA

CSF analysis and culture on admission- Clear and colourless; WBC nil, RBC nil; Protein 177mg/dl; glucose 2.1mg/dl (random blood glucose 8.0mg/dl); Gram and ZN staining: Negative. Routine culture: No growth (Note: there was no facility for *Mycobacteria* culture).

Blood culture: Staphylococcus aureus sensitive to erythromycin, ceftriaxone and ciprofloxacin.

Gastric aspirate for acid and alcohol fast bacilli (x3): Negative.

Electrolyte and urea Na-142mmol/L, K-4mmol/L, Urea- 3.9 mmol/L

Fine needle aspiration cytology (FNAC) of specimens obtained from left submandibular and axillary nodes and a right inguinal node: Inflammatory cells only.

Lymph node biopsy showed effaced architecture with numerous granuloma consisting of aggregated epithelioid cells and inflammatory cells. Areas of caseation were also seen.

Bone marrow aspiration showed increased myelopoiesis with preponderance of mature neutrophils. Plasma cells and lymphopoiesis were normal. Megakaryospoiesis was increased.

Chest X-ray showed homogenous opacity in the right lower zone of the lung.

Abdominal ultrasound revealed mesenteric and para-aortic lymph node enlargement but no ascites.

A working diagnosis of acute myeloid leukaemia (AML) with central nervous system (CNS) involvement was made. The differential diagnoses were Burkitt lymphoma and disseminated TB. The patient was commenced on ceftriaxone 100mg/kg/day and mannitol 1g/kg 8 hourly. Table 1 shows the results of investigations carried out. Based on the lack of evidence for AML and lymphoma, a therapeutic trial for TB with first line standard drugs was started a week after admission and prednisolone 2 mg/kg/day was also given in two divided doses. Phenobarbitone at 10 mg/kg loading dose, and 5 mg/kg/day in two divided doses was also started. He soon became brighter, the cervical nodes became smaller in size, and he was able to tolerate tube feeding. However, two weeks after admission, he became unconscious with a Glasgow coma score of 8 and a left seventh nerve paresis was noted. Meanwhile, the results of the lymph node biopsy carried out earlier became available and the histology showed evidence of TB adenitis; a diagnosis of disseminated TB with TB meningitis was therefore made followed by the commencement of a full course of anti-TB drugs namely, rifampicin (R)10mg/kg/day, isoniazid (INH) 10mg/kg/day, pyrazinamide (Z)25mg/kg/day and streptomycin (S)20mg/kg/day. Ethambutol was added after two months of therapy with the other four drugs.

About two months after admission, new lymph nodes were noticed in the cervical, inguinal and axillary areas, while previously palpable nodes that had become smaller initially, were once again getting bigger. Lentiviral screening done twice, two months apart, were negative. Despite the completion of the initial phase of therapy and completion of six weeks of prednisolone, he continued to deteriorate. During the course of admission, he had varicella which led to high grade fever that responded to paracetamol. In the last five days before death, he had irrational speech, increasing abdominal distension, worsening respiratory distress and copious discharges from the sites of lymph node biopsies (Fig. 1). He died after three months and 10 days of hospitalization.

Discussion

Tuberculosis (TB) remains an important cause of mortality and morbidity and is of interest to both the clinician as well as the public health practitioner. For this reason, there is a global effort directed towards the control of TB coordinated by World Health Organisation (WHO) with funding from both the private and public sectors. One of the reasons for the increasing menace of TB is the emergence of MDR strains. Unfortunately, the global approach for the control of TB (DOTS) does not incorporate drug susceptibility testing (DST) and this remains a major challenge for the TB control programmes in areas of the world where the disease is most prevalent, Nigeria inclusive. The DOTS-plus strategy tries to address MDR-TB but is not widely implemented.[7]

The protean nature of the clinical presentation of TB is highlighted by this 13-year-old boy who had features which closely resembled those of AML and Burkitt lymphoma both of which are common childhood malignancies in Nigeria.[8-10] Haematological investigations including a bone marrow aspiration, as well as fine needle aspiration cytology of the lymph nodes showed no abnormal cells to suggest these

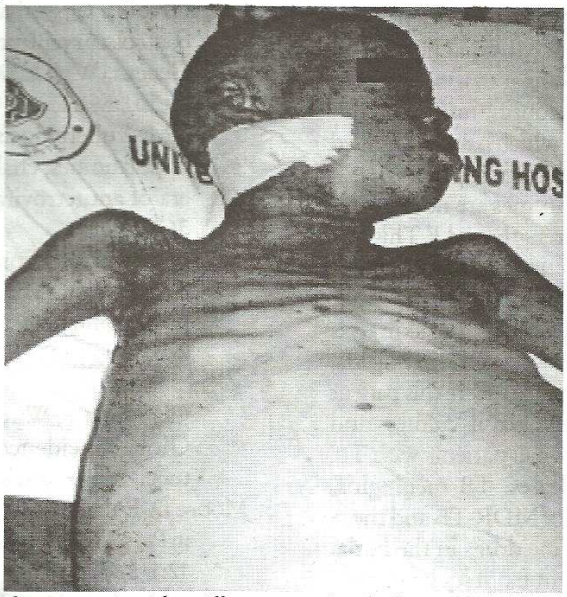

Figure 1: Peripheral lymph nodes are seen in right axillary, cervical and submandibular regions. The dressing is over the site of the lymph node biopsy that was discharging pus. There is wasting and abdominal distension. The healing lesions of varicella are obvious in the picture.

malignancies. Disseminated TB with superimposed acute bacterial septicaemia was then considered despite the laboratory's failure to obtain AAFB from gastric aspirates which was not unusual in the paediatric age group. The presence of significant weight loss, significant peripheral and abdominal lymph node enlargement, reduced breath sounds as well as the episodes of seizures in a Nigerian child justified the possible diagnosis of disseminated TB.[8] This was confirmed by the lymph node histology. A four-drug regimen, RINHZS, was commenced and given for two months before ethambutol was added at continuation phase because of poor response. In addition, a six-week course of corticosteroid was given. The very transient initial improvement noted in the patient might have been due to the added steroid. Thereafter, the patient showed no response to therapy as he continued to deteriorate. Screening for HIV was negative on admission and at two months after admission. The patient's failure to respond to the appropriate first line drugs in adequate doses given for a reasonable period of time and his subsequent deterioration led to a diagnosis of possible MDR-TB. Mycobacteria other than tuberculosis were also considered as the possible causes of the disease in this patient but were less likely in the absence of HIV infection.[11]

The dearth of literature on MDR-TB from Nigeria is not surprising because the diagnosis and management of MDR-TB require sophisticated laboratory support which is rarely available in Nigeria. However, MDR-TB has occurred in areas of the world where compliance with WHO guidelines for control are not strictly adhered to either with regard to the drugs used or other DOTS components; this makes Nigeria a likely place for MDR.[7] The story of TB control in Nigeria is very similar to those of other public health measures such as routine immunization and safe motherhood initiative which have had limited successes. This is because the appropriate health systems to support the programmes are not in place or they urgently need to be strengthened.[12] This fact also applies to the clinical practice where inadequate laboratory support makes the diagnosis of TB difficult even in tertiary centres. Simple tuberculin skin tests are not universally available in most centres in Nigeria, and were not available at our centre where this patient was managed. We believe that even if cultures and DST are not made available for all patients with TB, those with disseminated diseases, TB meningitis, pericarditis, contacts of cases of MDR-TB and those who do not respond to first line drugs in the initial phase of therapy should benefit from such facilities. Several functional regional and a national reference laboratory which could collaborate with more sophisticated centres abroad for molecular fingerprinting and polymerase chain reaction (PCR) for defining molecular markers of resistance are a necessity for the adequate control of TB in Nigeria. There is increasing evidence that a simple and inexpensive method, the microscopic observation drug susceptibility assay (MODS), can be effectively used in parts of the world where TB is endemic and resources are poor.[5] If drug resistant and MDR strains are not promptly identified and their spread interrupted, they have the potential to increase the mortality from TB. The implication of MDR has been well modelled by experts who suggest that even though the MDR strains are heterogeneous in fitness, they can, even in cases of limited transmissibility, constitute significant public health threats in future.[13,14] This fact is even more important with the presence of large number of cases with HIV. Treatments of MDR-TB with second and third line drugs are recommended but cure rates are better with individualized treatments. All of these are rarely available in our setting.

Conclusion

There is little doubt about the importance of MDR in TB control and the challenges of meeting its diagnosis and treatment. While the whole world focuses on DOTS to achieve its goals, the neglect of MDR-TB will be a serious setback in the bid to eliminate TB. The health systems and human resources in Nigeria need to be strengthened to prevent and combat MDR-TB by effectively implementing DOTS and DOTS-Plus.

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