Post Kidney Transplant Tuberculosis in Nigeria: A Case Report

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ABSTRACT

Background: *Tuberculosis has been reported to be one of the most serious bacterial infections after transplant and occur up to 20 times more frequently in transplant recipients than in the general population. Renal transplant is available in few centers in the country and the post transplant population is increasing, but to our knowledge no case of post transplant tuberculosis has been reported in this environment.*

Method: *The case report of a 35 year old Nigerian who had live related kidney transplant and later developed post transplant disseminated Tuberculosis is presented and the relevant literature is reviewed.*

Results: *A 35 year old university graduate had a live related kidney transplant in our center. He had stable allograft function on immunosuppressive regimen consisting of Cyclosporin, Azathioprine and Prednisolone, and presented with features of disseminated tuberculosis involving the cervical lymph nodes and chest with associated deterioration of allograft function. He was successfully treated with 2 months initial phase of quadruple anti tuberculosis drugs including Isoniazid, Rifampicin, Pyrazinamide and Ethambutol and four months continuation phase with Isoniazid and Rifampicin. He showed remarkable clinical improvement and reversal of the allograft dysfunction.*

Conclusion: *This case illustrates one of the post transplant infectious complications seen in our environment and its successful treatment, and highlighted the need for Tuberculosis prophylaxis in transplant recipients in countries with high incidence of tuberculosis.*

Key Words: *Tuberculosis, Kidney transplant, Nigeria*
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INTRODUCTION

In comparison with the general population, end stage renal disease, dialysis and renal transplant patients are reported to be at an increased risk for both primary and reactivation of Mycobacterium Tuberculosis infection. This is related to the fact that both uremia and iatrogenic immune-compromised state post transplantation contribute to the decrease in cellular immunity seen in these patients.

Tuberculosis is a serious opportunistic infection which may develop at any time after transplant but in most instances occurs during the first few months post transplant, when immunosuppression is maximal. The diagnosis may be challenging due to peculiarities in the clinical presentation in these patients. Although treatment modality is not different from that in the general population, certain factors must be considered such as the potentials for drug interaction and possibility of enhanced drug toxicity.

CASE SUMMARY

The case is that of a thirty one year old university graduate who had end stage renal disease from chronic glomerulonephritis and maintained on thrice weekly haemodialysis through an arterio-venous fistula. He was also receiving antihypertensive drugs (Lisinopril, Nifedipine), intravenous iron and erythropoietin among other medications. He had a successful living related kidney transplant in Aminu Kano Teaching Hospital in October 2003. Prior to the transplant he had a complete pre transplant workup which included a chest radiograph and a Mantoux test which were found to be normal.

He enjoyed a stable allograft function with no rejection episode on immunosuppressive regimen consisting of Cyclosporin, Azathioprine and Prednisolone but was not placed on anti tuberculosis prophylaxis. He was discharged four weeks post transplant (usual period which we discharge patient that are referred to us from long distance places) with normal serum creatinine and other biochemical parameters, and followed up on out patient basis.

His baseline renal function has been normal during follow up before he took ill.

Four months post transplant, he presented with three weeks history of recurrent fever and cough of one week duration, which was initially dry but later became productive of whitish sputum, but no haemoptysis. He also had significant weight loss, but no symptoms of cardiac decompensation or gastrointestinal tract symptoms. There was no history of contact with person with chronic cough. No change in urinary frequency or volume and no other genitourinary symptoms.

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Clinically, the patient looked ill and febrile (T = 38.5 °C). He was not pale, acyanosed, anicteric and no pedal edema. There was a palpable supraclavicular lymph node on the left that was firm, mobile, not attached to the overlying skin and approximately 4 5 cm in diameter. He was not dyspnoeic with a respiratory rate of 12 cycles per second. There were dull percussion notes with bronchial breath sounds and scanty crackles in the mid and lower zones posterioly in both lung fields. Other features of systemic examination were not remarkable.

Review of his investigation results showed a chest radiograph with bilateral widespread reticulonodular shadows. Percutaneous aspiration biopsy of the left supraclavicular lymph node, yielded 0.5 mls of purulent material and microscopy showed caseous necrosis with teaming acid-fast bacilli (AFB $^{+++}$) on Zeihl- Nielsen (ZN) stain. Sputum microscopy, culture and sensitivity as well as acid fast bacilli on ZN stain were unremarkable. The serum creatinine was 660 mol/l, urea was 10.3mmol/l, urine analysis was negative for protein, serum cyclosporin level (C2 level) was 1026 ng/ mls and serum electrolytes as well serum bilirubin and liver enzymes were all within normal limit, urine microscopy was unremarkable. Allograft ultrasound scan was essentially normal, but allograft biopsy was not done. An impression of disseminated tuberculosis (DTB) (chest, lymph node) with allograft dysfunction was made.

He was commenced on quadruple anti TB drugs including Isoniazid (INH), Pyrazinamide Rifampicin and Ethambutol. He showed remarkable improvement with regression of the lymph node enlargement, resolution of the chest signs and the pyrexia over a period of four weeks. Renal function also improved remarkably, with the urea becoming 7.1 mmol/ l, creatinine 225 mol/l. His serum C2 level, serum bilirubin and liver enzyme tests remained normal. He was discharged home after 30 days and has remained clinically stable with good allograft function after completion of six months anti TB therapy. Renal function at discharge was normal and has remained so as at the last follow up, six months after completing anti tuberculous therapy.

DISCUSSION

Tuberculosis is a serious opportunistic infection in renal transplant recipients. It can be diagnosed at anytime after transplantation, but in many instances, it occurs during the first few months post transplant, when immunosuppression is maximal. This patient presented four months post transplant.

The risk of developing TB in transplant recipients is directly related to the general epidemiological risk of the condition in the environment, for example, the incidence in transplant recipients in the US has been reported to be between 0.35% and 1.3%, and 0.84 % in Spain.[1] In contrast, in countries with high rates of TB in the general population, its incidence in transplant patients is much higher; 3.5% in Saudi Arabia, 11% in South Africa, 11.8 % in India and 14.5% in Pakistan.[2] In Nigeria, the incidence in transplant recipients is not known but going by the high incidence of TB in the community, one may not be surprised if it turns out to be similarly high.

Tuberculosis in transplant recipients may arise from transmission via the donor kidney, but these cases are rare and account for less than 5% of the TB infections. Contamination by actively infected persons through air borne spread in the community can also occur, but it is assumed that, the vast majority of active TB infection in transplant recipients develops from reactivation of quiescent form of TB that persisted after an initial contamination (latent TB infection).[3]

Clinical presentation of TB in transplant recipients may not defer from that seen in the general population. However, the immunosuppressive state of the patient may hamper the control of the infection and which is frequently disseminated and dissemination of the disease is reported to occur in 40-60 % of cases compared with 0.6 1.4 % in the general population.[4] This patient had disseminated infection at the time of diagnosis. He also had associated allograft dysfunction with no other features of acute rejection such as reduced urine output, allograft tenderness and proteinuria. Acute rejection may not be ruled out as renal biopsy was not done at the time of presentation because the patient was very ill. Allograft dysfunction was reported in 29 % of post transplant TB at the time of diagnosis in Taiwan.[5] The possible contribution of TB infection to the incidence of graft dysfunction and acute rejection remains unclear.[6]

Although in this patient the diagnosis was easily arrived at, diagnosis of post transplant TB can be very challenging and should be aggressively sought for in transplant patients suspected to be having the infection, even in the presence of unusual manifestation. The caseation and tissue destruction that lead to cavitations is not frequently seen as this requires a robust immune response which is not present in transplant recipients. Sputum smear positivity is low while tuberculin reaction is unreliable in the diagnosis of latent TB infection in this group of patients. Culture results take too long for adequate decision making in the clinical setting and are not readily available in most centers in developing

countries. As a result of these limitations there is growing interest in using sensitive and rapid tools for TB diagnosis in places where such facilities do exist, such as measurement of Adenosine deaminase levels in the appropriate specimens and molecular methods like PCR which allow for the diagnosis of TB on the same day that specimens are collected. Fine needle aspiration cytology is a simple, cheap and rapid test with high accuracy, specificity and sensitivity that can be carried out in limited resource settings. It facilitated prompt diagnosis in our patient even though sputum examination had not detected the infection.

According to European Best Practice guidelines (EBPG), the treatment of active TB infection in renal transplant recipients should be the same as in the general population i.e. two months of quadruple therapy combining Rifampicin, INH, Ethambutol and Pyrazinamide, followed by a four months double therapy with INH and Rifampicin.[4] The same regimen was used in the management of this patient and there was adequate response consistent with reports in the literature that greater than 90% of transplant patients treated with classical anti TB drugs for at least six months achieve a microbiological cure without relapses.[1,7] Even though the treatment does not differ from that of the general population, it is associated with peculiar problems. One important consideration is the potential for drug interactions. Rifampicin is an inducer of cytochrome p450 microsomal enzymes, which can lead to reduced blood levels of calcineurin inhibitors, rapamycin and steroids. This can trigger acute rejection and in some series up to 30% incidence of graft rejection and 20% incidence of graft loss were reported.[7] It is recommended that serum level of calcineurin inhibitors be monitored and dosage adjustments made as appropriate in these patients so as to avoid acute rejection. It is of note in this patient that the C2 level was monitored during the treatment period and he needed no dosage adjustment. The other issue is the possibility of increased hepatotoxicity of INH in transplant recipients. The American Thoracic Society recommends the discontinuation of INH only when asymptomatic patient displays alanine transferase or aspartate transaminase levels above 3-5 times the upper limit of the normal.[8] Data about the hepatotoxicity in renal transplant recipients are limited however a multicenter retrospective analysis showed that 4 out of 33 patients (11%) had to discontinue INH because of hepatotoxicity.[1] In this patient serial bilurubin and liver enzymes tests were done and no significant rise in the enzymes were noted.

A joint statement of the American Thoracic Society and Center for Disease Control has defined a latent TB infection and recommends that, patients with organ transplants and those with chronic renal failure who have latent TB should be treated.[8] The preferred treatment of latent TB infection is INH 300mg daily for 9 months. Other alternative therapies include Rifampicin and pyrazinamide daily for 2 months or Rifampicin alone for 4 months.

Whether INH prophylaxis changes the prevalence of TB post transplant still remains controversial. In the series reported by Higgins et al [9] there were no cases of TB infection among those who received prophylaxis. There were two different studies which showed that the prevalence of post transplant TB was not changed by the administration of INH prophylaxis.[10, 11] These controversies arise because there are no adequately powered, randomized controlled trials to determine the efficacy of the treatment. Despite these, it has been the practice of many transplant centers to give INH prophylaxis where it is indicated. This should be more relevant in areas of high prevalence like the tropical countries.

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