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Extrapulmonary Mycobacteria Tuberculosis Infection in Kidney Graft Recipient: Case Report and Literature Review

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Abstract

We present N.K, a 31-year old male from Kenya, East Africa, who is a kidney graft recipient from 2013. He suffered endstage kidney disease from poorly controlled hypertension. Subsequently was transplanted from a living related haploidentical donor. He presented barely two years later with asthenia, general body malaise and back pain. He was diagnosed with an abscess in the transplanted renal bed in the right iliac fossa, which yielded *Mycobacteria tuberculosis* on polymerase chain reaction, which was rifampicin sensitive. We started him on an anti-TB regimen which include isoniazid, pyrazinamide, ethambutol and moxifloxacin. Tuberculosis poses diagnostic and treatment challenges in transplant recipients. Balancing between drug-drug interactions, and raising immunity without adversely affecting the kidney graft is paramount.

Keywords: Kidney transplantation; Kidney graft recipient; *Mycobacteria tuberculosis* infection in transplant recipients.

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1. Introduction

N.K. was 27 year-old male by the time he was referred to a nephrologist in 2011 by a physcian. He was referred with diagnosis of chronic kidney disease probably from chronic glomerulonephritis with target organ damage. He was on nifedipine 40 mg twice daily, furosemide 40 mg once daily and carvedilol 12.5mg twice daily. He had developed hemiparesis a month prior to presentation to the nephrologist. Conservative management for the chronic kidney disease was continued with intensification of blood pressure control. In April 2013, arterio-venous fistula was created in the left antecubital in anticipation for dialysis which he started later. In October 2013, he got kidney graft transplant, from living-related donor, female, 31 year- old, blood group O, rhesus positive, Human Leucocyte Antigen (HLA) mismatch 3/6. He was started on tacrolimus 2.5 mg twice, prednisone and mycophenolate mofetil 720mg twice daily. Peritransplantation period was unremarkable. In 2015 August, he presented with general ill-health, backpain, weight loss. In October 2015, he presented with fever, progressive weight loss for last 6 months from 70 to 50 kg, severe lower back pain with associated difficult in walking. Examination revealed tenderness at the lower back around fourth and fifth lumbar spines. Urinalysis showed leucocyturia, chest radiograph was normal. Radiograph of the lumbosacral region was unremarkable. Magnetic resonance imaging of the pelvis revealed lesion behind the graft kidney in the right iliac fossa..

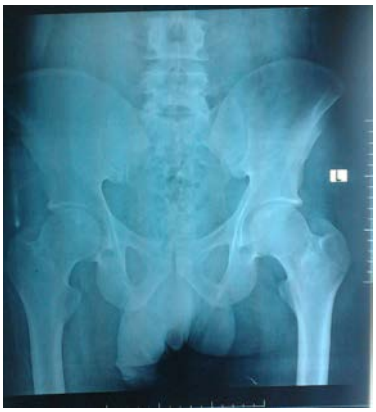

Figure 1: Chest radiograph

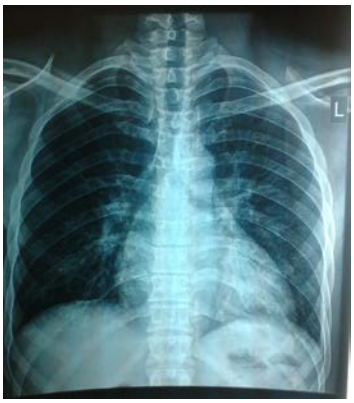

Figure 2: Pelvic radiograph

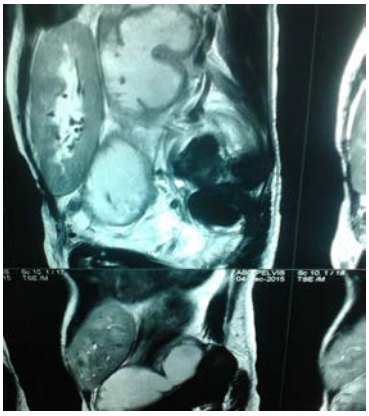

Figure 3: MRI Abdominopelvis

Ultrasound scan of the lumbar mass with aspiration yielded pus. Microbiologic studies: –Polymerase chain reaction for Mycobacteria: Mycobacteria detected which was rifampicin sensitive. Routine microscopy: scanty leucocytes and erythrocytes. No bacteria, no fungal elements seen. Bacterial cultures: Aerobic and anaerobic cultures: no growth obtained.

The kidney functions from February 2015 to October 2015 were: Sodium 121 – 137 mmol/L, potassium 3.5 - 4.3 mmol/L, urea 3.7- 7.94 mmol/L, creatinine 81-125 μmol/L. The haemogram parameters during this period were: Leucocytes counts: 6.62 -16.2 X 10^9/L, relative count of granulocytes from 63-76.7% and lymphocytes 16.8-29%. Erythrocytes counts were 5.28-6.34 X 10^{12}/L, mean corpuscular volume at 66.7 – 76.5fL, and haemoglobin levels 13.4 – 15.8 g/dL. The tacrolimus plasma trough levels ranged between 4 – 5.4 ng/mL.

N.K was initiated on anti-mycobacteria tuberculosis treatment with isoniazid 300mg, ethambutol 600mg, pyrazinamide1500 mg and moxifloxacin 400mg once daily in the intensive phase for two months with a plan to continue with ethambutol 600mg , isoniazid 300 mg and moxifloxacin 400mg for 10 months in the continuation phase, to cover a total treatment period of 12 months.

Three months after initiation of treatment, N.K has shown pleasant progress with renal functions, liver functions, blood counts, plasma tacrolimus trough levels, and general well being showing marked improvement.

His creatinine has ranged from 64 to 95 μmol/L, urea 5.5 to 9.0 mmol/L. The tacrolimus plasma trough levels have been between 4.4 and 9.6 ng/mL. He has generally showed marked improvement and the pain subsided. His tacrolimus dose had been 1.5mg twice daily.

2. Discussion and Literature Review

Tuberculosis (TB) has plagued humankind for thousands of years worldwide. It is likely to have existed in prehominids. John Bunyan (Nov 28, 1628–Aug 31, 1688), described tuberculosis as “The Captain among these men of death” at a time when tuberculosis case rates in London had reached 1000 per 100 000 population per year [1]. Risk factors which have been documented for development of tuberculosis include human

immunodeficiency virus infection which increases the risk by 20 – 37 times depending on country HIV prevalence [2, 3]. Diabetes mellitus type 1 increases the risk of TB infection by about 3 times [4, 5], end-stage renal failure increases the risk by more than 10 times [6], solid organs and haematological malignancies associated with increased risk [7, 8] while corticosteroid therapy increases the risk by about two times [9]. N.K had chronic kidney disease, later he was on corticosteroids since 2013 and this could have predisposed him to developing TB. The commonest form of tuberculosis is pulmonary, although for N.K, no pulmonary focus was evident. Extrapulmonary TB posses a more difficult diagnostic challenge when compared with pulmonary TB. However, pulmonary tuberculosis is more common (almost twice) in non-transplant recipients than in transplant recipients. Disseminated tuberculosis is more frequent in transplant recipients (five times more) when compared with non-transplant patients [10]. Comparison of tuberculosis in transplant and non-transplant found three times more factors predisposing transplant recipients to TB when compared with non-transplant non-HIV cases. Time from clinical suspicion of tuberculosis to definitive diagnosis was longer in transplant recipients than in non-transplants. Invasive procedures were three times more required in transplant recipients than in non-transplants [10]. This was the case for N.K, where the chest radiographs were unremarkable and had no sputum production. The diagnosis was got from pus drained from the grafted kidney bed abscess.

In solid organ recipients, while TB may be donor-transmitted or community-acquired, it usually develops at a latent infection site in the recipient. *Mycobacterium tuberculosis* can be transmitted by transplantation which has been estimated previously to account for 4% of the reported post-transplant TB cases [11]. For N.K. the donor had N.K. were both screened for pulmonary tuberculosis before transplantation, which were negative.

Immunosuppression with one or both of tacrolimus and mycophenolate mofetil has been associated with the development of TB at a younger age and at a higher frequency during the first 6 months after transplantation when compared with conventional therapy [12]. N.K had been on both tacrolimus and mycophenolate mofetil.

The major immunosuppressive agents that are currently being used are corticosteroids (oral prednisone), azathiaprine, or mycophenolate mofetil and cyclosporine or tacrolimus. The optimal dose of maintenance immunosuppressive therapy in renal transplantation has not been established. The incidence of opportunistic infections increases when such potent agents are used. In a large European trial, treatment with cyclosporine and tacrolimus was associated with the development of infection in about 40% of patients, sepsis in 20% and cytomegalovirus infection in 15–25% [13].

2.1 Prevalence of tuberculosis in transplant recipients

The prevalence of tuberculosis in transplant recipients is higher than in general population. Solid organs transplantation (SOT) is a well established predisposition to development of TB. Development of TB infection in SOT recipients occurs in the first year post-transplantation [14] in most cases, but a bi-modal distribution has also been observed, with the incidence of TB at a peak 2 years after SOT[15, 16]. In Europe, the incidence of TB in solid organs transplant (SOT) recipients has previously been reported to be as high as 3.5% [17], lower rates have been reported recently (0.45–0.9%), [14, 18, 19]. The highest incidence (6.4–10%) has been observed in lung transplant recipients [20-22]. The percentage of SOT recipients who develop extrapulmonary or

disseminated TB is higher than in the general population [11, 16, 18, 23]. The incidence of TB among organ recipients is as much as 74- times that of the general population [11]. In 14 French transplant centres, between 1986-2006, among 16146 kidney transplant recipients, 0.45% developed TB. Extrapulmonary and disseminated TB accounted for 67.4% of cases. The most common symptoms were fever (71.7%) weight loss (41.3%) and asthenia (39.1%) [24]. All these were present in N.K. In India, Post-transplant tuberculosis has been reported to occur in 12 to 20% of patients, and results in 20 to 25% of those patients [25]. In Tunisia, from 1986 to 2009, among 491 renal transplant recipients, the prevalence of TB was 3.2 % with an overall incidence of TB being 72/100 kidney transplant recipient/year, whose presentations were sterile leucocyuria, graft dysfunction and biological inflammatory syndrome [26]. Pulmonary TB was noted in more than 60% of the cases, with extrapulmonary in almost 20% in this population.

2.2 Clinical presentations

In SOT recipients, symptoms of infection are often attenuated, leading to delayed diagnosis. The most common symptoms are fever, weight loss, and asthenia [24]. Diagnosis of extrapulmonary TB is difficulty of to make, which often leads to empirical treatment without pathological or bacteriological confirmation [27]. In developing countries, the problems of diagnosis are compounded by a lack of diagnostic resources. TB may not be considered at all in the differential diagnosis, resulting in delay or deprivation of treatment [28]. Extrapulmonary forms of tuberculosis occur in all age groups, adding to diagnostic and treatment difficulties. Clearly, it took time for us to make the diagnosis in N.K.

2.3 Latent tuberculosis infection

Latent TB infection (LTBI) is infection with Mycobacteria Tuberculosis Complex (MTC) at an early stage with viable organism in a dormant state. There lacks a reference standard to diagnose LTBI. Diagnosis is usually made by documenting a positive tuberculin skin test (TST) in a person who has no signs, symptoms or chest radiograph evidence of active TB disease [29]. False-negative TST results occur in anergic patients, such as those receiving immunosuppressive therapies and/or affected by chronic kidney and liver disease, and this excluded using TST in N.K. False-positive results occur in areas in which Bacillus Calmette–Guérin (BCG) vaccination is prevalent or when there is accidental exposure to environmental non-tuberculous mycobacteria (NTM), this too excluded TST from being used for diagnosis in N.K.

Novel blood tests have become available which detect gamma interferon production in response to antigens encoded by the section of MTB DNA called region of deletion 1 (RD1), which is present in virulent MTB strains but is deleted in all attenuated *Mycobacterium bovis* BCG vaccine strain genome [30]. These tests, now known as interferon gamma release assays (IGRAs). They are more specific (presenting no cross-reactivity with BCG and NTM) and less affected by immunosuppressive therapies, despite undergoing the same inhibition of immune mechanisms that is responsible for the impaired performance of TST. Two commercially produced IGRAs are available. Both tests employ a mitogen-induced positive control able to differentiate between an anergic and a true negative response. With both tests, the result may be reported as qualitative (positive/negative) or quantitative according to defined cut-off values. Quantitative results seem more accurate

in detecting the progression of TB infection [31-34]. Interferon gamma release assays presented higher positivity than TST and provided a more accurate reflection of the risk of LTBI among kidney transplant candidates [35] and also showed a role in predicting subsequent TB development in kidney transplant recipients in whom TST did not detect LTBI [36]. Use of interferon gamma release assay and tuberculin skin test for diagnosis of latent tuberculosis infection in kidney transplant recipients showed reasonable concordance but no superiority of either test [37]. Tuberculosis is a very serious complication in SOT recipients and both TST and IGRAs may have false-positive and negative results, however, their concurrent use would be the ideal approach for increasing diagnostic sensitivity [34]. IGRA was negative for our patient N.K.

2.4 Active TB

A diagnosis of TB can only be confirmed by culturing MTC or by identifying specific nucleic acid sequences in a clinical specimen collected from the suspected site of disease, with culture being the most sensitive detection method. Growth is necessary for definitive species identification and full drug susceptibility testing (DST) [38].

2.5 Treatment of Active TB in Pre-transplant

For the purposes of treatment, extrapulmonary tuberculosis can be classified into severe and non-severe forms. Severe forms include meningeal tuberculosis, spinal tuberculosis, neuro-tuberculosis, abdominal tuberculosis, bilateral pleural effusion, pericardial effusion, and bone and joint tuberculosis involving more than one site. Extrapulmonary tuberculosis of other sites is classified as non-severe [39]. In SOT recipients no efforts should be spared in search for TB. When active TB cannot be ruled out, the worst case scenario should be assumed and initiation of TB treatment with the standard three drugs. If cultures for MTC are negative after the 8^{th} week of incubation, treatment can be completed with isoniazid alone [40]. Patients with active TB should not undergo transplantation.

2.6 Treatment of Active TB in Post-transplant

The adverse effects of TB therapy present a major difficulty, due to the interactions with immunosuppressive drugs and direct drug toxicity [41]. A standard 6-month regimen including rifampicin for TB treatment, in accordance with the currently available guidelines for the general population [42, 43]. It is reasonable to use a prolonged course of treatment in the immunosuppressed SOT population [40]. For N.K. we choose to treat him for 12 months. However, there are no randomized controlled trials assessing the optimal schedule and duration of TB therapy in SOT recipients so far. Treatment of TB in SOT differs from that of general population in several aspects. The interactions between rifamycins and immunosuppressants, and the potential for hepatotoxicity associated with first-line TB therapy [40]. Many first-line anti-TB drugs (isoniazid, streptomycin and ethambutol) warrant dose adjustment in renal transplant patients. The use of rifamycins remains controversial. The interaction between rifampicin and calcineurin inhibitors, inhibitors of the mammalian target of rapamycin (mTOR) and corticosteroids is known to increase the risk of acute rejection [44-48]. The use of rifampin has been identified as a risk factor for immune reconstitution syndrome (IRS) related to changes in immunosuppressive treatment [49] though studies in populations other than SOT recipients have shown an

increased risk of TB recurrence and high TB resistance rates when rifamycin-sparing regimens are used [43, 50]. There are difficulties adjusting immunosuppressive drug serum levels and a high graft failure rate with rifampicin usage [51-53]. For these reasons, we chose to omit rifampicin in our treatment regime for N.K. Recent series have observed no difference in post-tuberculosis rejection rate or mortality between patients who did or did not receive rifampicin-based regimens [14, 54] and these drugs may be safe with rigorous control of immunosuppressive drug levels [17, 55, 56]. In HIV patients, rifabutin appears to be as efficacious as rifampicin, thus, it might be an alternative in SOT recipient and has shown fewer interactions with immunosuppressive drugs [40]. The benefits of rifamycins must be balanced against the risk of rejection. Physicians may weigh the risks and benefits before including rifamycins in the anti-TB regimen in SOT recipents. If rifampin use is mandatory, the dose of calcineurin inhibitors and mTOR should be increased between three and five-fold (increasing the frequency of administration from twice to thrice daily) and the corticosteroid dose should be doubled [11, 15, 44, 57-60]. Levels of immunosuppressants should be closely monitored for both kinds of rifamycins.

2.7 Regimens including rifamycins

In rifampicin- or rifabutin-containing regimens, a standard treatment based on a three-drug regimen may be considered with the exception of high isoniazid-resistant regions. Completing treatment with isoniazid and rifampicin or rifabutin in the maintenance phase for at least 9 months is rational [40], for treatments duration less than 9 months have been associated with an increased mortality rate [15], while a 9–12 month period of anti-tuberculosis treatment have been shown to reduces the risk of recurrence or treatment failure rates [55, 61]. When regimen of isoniazid, rifampin and pyrazinamide are used, hepatic function monitoring is mandatory as these drugs may cause significant hepatotoxicity [15, 43, 61-63]. Pyrazinamide could be replaced with a fluoroquinolone in shorter course regimen. Extended treatment duration of 12-18 months have been suggested in patients with cavitory pulmonary TB whose culture remains positive after 2 months of treatment [40, 56, 64-66].

2.8 Regimens that do not include rifamycins

Voidance of rifamycins is a common practice in TB treatment in SOT recipients owing to the interactions of transplant drugs with rifamycins. If rifamycin-free therapy is used, prolonged treatment duration of 12-18 months has been considered for SOT patients due to the experience gained in the general population [11]. In rifamycin-free treatment regimens, a combination therapy with isoniazid and ethambutol for 18 months with the addition of pyrazinamide for the first 2 months has been proposed [57]. Maintenance agents may include isoniazid and pyrazinamide or ethambutol, and the possible addition of levofloxacin/moxifloxacin should be considered; a three-drug regimen may reduce the treatment length [40]. Favourable experiences with the use of isoniazid, pyrazinamide and ethambutol for the first 2 months, followed by a 12- to 18-month course of complete therapy have been reported [55, 67]. Fluoroquinolones (FQs) are an alternative for transplant patients because of the disadvantages associated with rifamycins and aminoglycosides [68]. In the transplant setting, good outcomes with FQs in the initial four-drug regimen for kidney and lung transplant recipients have been described [20, 69, 70]. The preliminary results of two quinolones-containing regimens, the RIFAQUIN trial (moxifloxacin and rifapentine twice weekly in place of rifampicin and isoniazid) [71] and the OFLOTUB trial

(gatifloxacin instead of ethambutol), showed the inferiority of 4-month TB regimens for outcome [72]. The possibility that the widespread use of FQs for other infections could lead to a high prevalence of FQ-resistant TB is a matter for concern [73]. Prolonged use of fluoroquinolones may be associated with arthralgias [16]; it may enhance the risk of tendon-related side-effects of corticosteroids, and a combination may decrease mycophenolate levels. Levofloxacin may increase cyclosporine levels [74]and its combination with pyrazinamide is associated with poor digestive tolerance [75]. Linezolid has proven to be effective for patients with TB [76], though prolonged use of this drug has been associated with thrombopenia, anaemia and polyneuropathy, especially in patients with diabetes or kidney disease.

2.9 Drug-resistant Tuberculosis

Multidrug-resistant (MDR) TB is defined as resistance to both isoniazid and rifampin and extremely drug-resistant (XDR) TB is defined as resistance to isoniazid, rifampin, fluoroquinolones and at least one injectable drug like mikacin, kanamycin and capreomycin [77]. Public health action is needed to improve treatment outcomes in regions where drug-resistant TB is prevalent [78]. Few case reports of MDR-TB in SOT recipients have been published [79-81]. In non-SOT individuals with MDR-TB infection, treatment with second-line anti-TB therapy for 18–24 months achieved a 75% long-term success rate [82]. If isoniazid and rifamycins cannot be used, induction treatment should include four to six drugs, including injectable antimicrobials. Evidence is lacking on the recommended treatment duration for these regimens, but up to 2 years following MTC culture conversion is reasonable [83].

2.10 Prevention of TB in Kidney transplant recipient

Cochrane review of on antibiotic prophylaxis for preventing post solid organ transplant tuberculosis found evidence in favour for TB prophylaxis administered to all kidney transplant recipients in TB-endemic regions during the first year post-transplant [84] .

3. Recommendations

Tuberculosis infections and organ transplantation require more evidence and long term follow up with close monitoring to maintain sufficient immunity without compromising the grafted organ function. Studies in among the transplant populations will shed more light into the complexity of the care in Tuberculosis treatment and immunosuppressive therapies.

4. Conclusion

Tuberculosis infection poses challenges in transplant population. The recipients are predisposed to the infection due to the primary disease like chronic kidney disease, treatment of the primary disease which include transplantation which makes the patients to be on long term immunosupression. Diagnosis of TB can be challenging in this population and may take protracted course. Treatment of the TB requires balancing act between the transplanted organ function and achieving cure without losing the patient to the disease. This is mainly due to drugs interactions. More studies are required in this field of transplantation and TB.

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