

Single Case

Rifabutin-Induced SIADH and Leucopenia in a Renal Transplant Recipient with Genitourinary Tract Tuberculosis: A Case Report and Review of the Literature

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Keywords

Hyponatremia · Leucopenia · Renal transplant · Rifabutin · Tuberculosis

Abstract

Tuberculosis (TB) infection of the genitourinary tract (GU TB) is rare in renal transplant recipients, with only a few published case series. GU TB is difficult to diagnose with or without immunosuppression but must always be suspected in any patient with unexplained sterile pyuria. As GU TB is associated with graft rejection, prompt diagnosis and treatment are vital. Treatment is challenging, as rifampicin, the most effective drug used to treat tuberculosis, is a significant inducer of cytochrome P-450 3A metabolism, with the potential to cause significant reductions in the serum levels of calcineurin inhibitors. For this reason, rifabutin, a weaker cytochrome P-450 3A inducer, with similar efficacy against TB, is sometimes used as an alternative to rifampicin in transplant recipients. We present a renal transplant patient diagnosed with GU TB, treated with a regime containing rifabutin, who subsequently developed profound hyponatremia and leucopenia. Serum and urine biochemistry was consistent with a diagnosis of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Both SIADH and leucopenia resolved with rifabutin cessation. This is the first report of biochemically proven, idiosyncratic SIADH and leucopenia associated with the use of rifabutin in the treatment of GU TB in a renal transplant recipient.

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Introduction

Tuberculosis (TB) is an infrequent complication post-renal transplantation. Prevalence ranges from 0.07% to 1.7% among Western Europe and North America to 2–13% in Asia [1]. Overall, the mortality rate among organ transplant recipients is 29% in the USA and 28% among those from Europe [2]. TB is more likely to develop in extrapulmonary sites such as the genitourinary tract in transplant recipients than in patients not taking immunosuppressive drugs [3]. Accurate prevalence of genitourinary tract TB (GU TB) in renal transplant recipients is unknown and limited to case series in the literature. Because of its atypical clinical presentation, diagnosis is more challenging in immunosuppressed patients, leading to a delay in diagnosis and treatment.

Use of rifampicin in the treatment of TB posttransplantation remains controversial and challenging. This is due to interactions between rifampicin and calcineurin inhibitors, leading to enhanced metabolism, subtherapeutic trough levels, and an increased risk of allograft rejection [4]. Increasing drug resistance and inadequate immune responses to *Mycobacterium tuberculosis* due to immunosuppressive agents, and the side effects of long-term treatment of TB, further complicate management [5]. Usage of rifabutin as an alternative to rifampicin is a hot topic in the treatment of TB post-solid organ transplantation [4, 6, 7]. Rifabutin is a weaker cytochrome P-450 inducer compared to rifampicin, with fewer immunosuppressant drug interactions, and has a similar therapeutic efficacy against *Mycobacterium tuberculosis* [8]. However, evidence of favourable outcomes using rifabutin in the treatment of TB posttransplantation is limited to small case series [8] and case reports [8, 9].

We describe a renal transplant patient diagnosed with GU TB treated with rifabutin, who subsequently presented with a collapse associated with profound hyponatremia and leucopenia. Syndrome of inappropriate antidiuretic hormone (SIADH) was the cause of hyponatraemia, with both SIADH and leucopenia resolving shortly after stopping rifabutin, confirming this to be an idiosyncratic side effect of rifabutin. In the literature to date, there is only one report describing suspected rifabutin-induced leucopenia and SIADH in an immunocompetent patient treated for *Mycobacterium avium complex* pulmonary disease [10]. This is the first report of this side effect being observed in a renal transplant treated for TB.

Case Report

A 66-year-old renal transplant recipient was diagnosed with GU TB in 2020. She was unaware of any active TB contacts during childhood, and received a deceased donor renal transplant in Newcastle, UK, in 2014 for renal failure secondary to hypertension. She was assessed to be at standard immunological risk receiving standard immunosuppressive induction with methylprednisolone and basiliximab followed by triple maintenance immunosuppression with tacrolimus, mycophenolate mofetil, and prednisolone. She also received 3 months of co-trimoxazole antimicrobial prophylaxis for posttransplant pneumocystis pneumonia. Although she was born in Guiana, she moved to the UK in 1976 aged 20 and had not returned to her country of origin since emigrating. Therefore, when she was transplanted 38 years later, she was not considered high risk and did not receive TB prophylaxis with isoniazid and pyridoxine posttransplantation. Past medical history included diet-controlled type 2 diabetes. Based on a detailed social and medical history including prior countries of residence and exposure, the deceased donor was considered low risk and did not have any microbiological investigations for TB.

In clinic, she reported several months of intermittent cloudy urine, dysuria, and frequency, associated with microscopic haematuria and persistent sterile pyuria. She had no constitutional

or respiratory symptoms, was afebrile with stable graft function, and had an unremarkable chest radiograph. Renal tract computerized tomography showed no abnormalities within the graft or native kidneys, with fat stranding around the bladder, consistent with inflammation. Flexible cystoscopy showed an inflamed bladder mucosa, consistent with cystitis. In view of the persistent sterile pyuria, GU TB was suspected, and early morning urine samples were sent for acid fast bacilli growing *Mycobacterium tuberculosis*, with a positive urine tuberculosis polymerase chain reaction. Further assessment showed this to be fully sensitive to first line TB drugs on whole genome sequencing.

Empirical treatment of GU TB was commenced, and initial treatment included rifabutin, isoniazid, and pyrazinamide, with vitamin B6 supplementation. Rifabutin was chosen instead of rifampicin to minimize inevitable interactions with tacrolimus.

Six weeks after starting TB treatment, she presented with collapse, initially thought to be secondary to vasovagal syncope. Serum sodium was low at 112 mmol/L (normal range 133–146 mmol/L), having been normonatremic 2 weeks prior. She received intravenous 0.9% sodium chloride, which improved serum sodium levels. She was discharged only to be readmitted days later with further vasovagal episodes and relapsed hyponatraemia at 129 mmol/L. Biochemical workup revealed hypotonic hyponatraemia with a serum osmolality of 259 mOsm/kg (normal range 275–295 mOsm/kg). Spot urine biochemistry demonstrated relatively concentrated urine with an osmolality of 283 mOsm/kg and a urine sodium concentration of 68 mmol/L, satisfying biochemical criteria for SIADH. Adrenal insufficiency and thyroid dysfunction were ruled out biochemically, and graft function was stable (creatinine 1.42 mg/dL). The patient was clinically euvolaemic and not taking any diuretic medications. New leucopenia was also noted with a white cell count of $2.33 \times 10^3/\mu\text{L}$.

Investigations for SIADH included a CT head, chest, abdomen, and pelvis with no lesions identified to explain the SIADH. As the patient completed 2 months of pyrazinamide, this stopped, and she continued rifabutin and isoniazid.

Rifabutin was the suspected cause of both the SIADH and leucopenia, and was stopped and substituted with rifampicin, with careful monitoring of tacrolimus trough levels and corresponding tacrolimus dose adjustments. Interestingly, hyponatremia improved but persisted (sodium 128 mmol/L) despite stopping rifabutin. Endocrine workup revealed a relatively dilute urine output (urine osmolality 186 mOsm/kg) compared to serum tonicity (serum osmolality 276 mOsm/kg). This biochemical pattern was suggestive of water excess, and it transpired that the patient had increased their daily fluid intake substantially following the vasovagal episodes. She was advised to restrict to 1.5 L/day fluid and serum sodium normalized (134 mmol/L) thereafter, as shown in Figure 1. White cell counts improved promptly after stopping rifabutin, as shown in Figure 2. She completed a 9-month course of TB treatment, including rifampicin and isoniazid, following negative TB urine cultures and resolving bladder inflammation on CT imaging, with stable graft function and no episodes of rejection.

Discussion

Immunosuppressed renal transplant recipients have an almost fifty-time increased risk of developing opportunistic infections such as TB [11], compared to the general population. The prevalence of TB among renal transplant recipients varies widely in different parts of the world [6]. Predisposing risk factors include age over 60, diabetes, corticosteroids, tacrolimus, T cell depleting immunosuppression, radiological evidence of previous untreated pulmonary TB, and presence of other coexisting infections including cytomegalovirus and *Pneumocystis jirovecii* [6, 12, 13]. Knowledge of both the donor and recipient's history is important in assessing TB risk and providing appropriate prophylaxis [14].

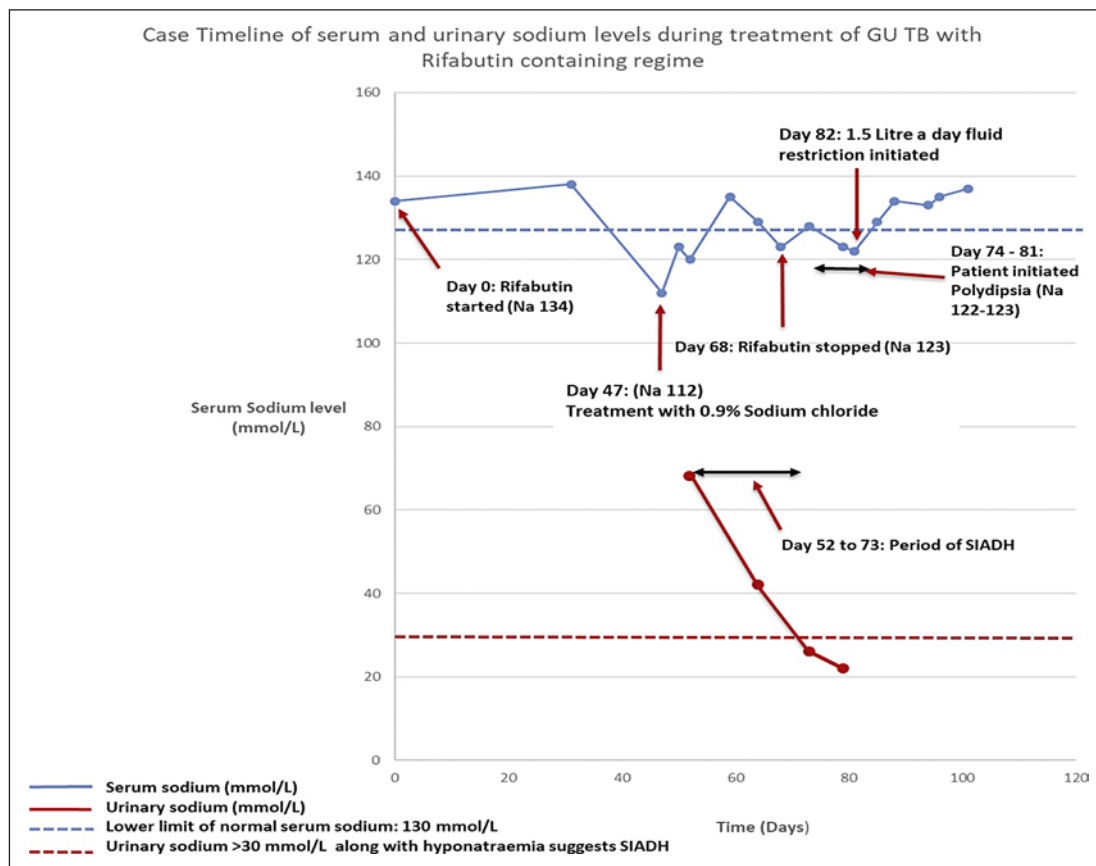


Fig. 1. Timeline of serum and urinary sodium levels during treatment of genitourinary tract TB using a rifabutin-containing TB treatment regimen.

Our patient was over 60, born in an endemic TB region, with diabetes on chronic corticosteroid and tacrolimus immunosuppression, and with unremarkable chest radiographs pre- and posttransplantation. She was not screened for TB prior to transplantation with an interferon gamma release assay or tuberculin skin test. The most likely explanation for developing GU TB was reactivation of a previous TB infection due to an immunosuppressed status. TB isolate did not match other cases in the Public Health England whole genome sequencing database, ruling out recent “transmission” from another (living) person in the UK. We also suspect that TB infection was not transmitted from the renal donor since there was no radiological evidence of TB infection in the graft and it developed within the bladder wall. Primary infection is also less likely based on the clinical presentation and low incidence of primary acquired TB infection in the UK.

TB posttransplantation typically occurs within the first year of transplantation in kidney recipients [1]. Pulmonary disease is most commonly seen, followed by involvement of the genitourinary tract [3]. Our patient was 6 years posttransplant when urinary tract symptoms developed.

Presentation of GU TB posttransplantation differs from GU TB in nontransplant patients, with fewer genitourinary symptoms [13]. The most common laboratory finding in GU TB is sterile pyuria [1]. Other features include haematuria, progressive renal impairment, fever, and nonspecific constitutional symptoms [13]. This can lead to a delay in diagnosis and treatment with a mortality of up to 18% in transplant recipients with TB [15]. A recent systematic review of over 2,082 cases of TB post-solid organ transplantation reported only 72 cases of GU TB post-renal transplantation in the literature over the past 45 years [14].

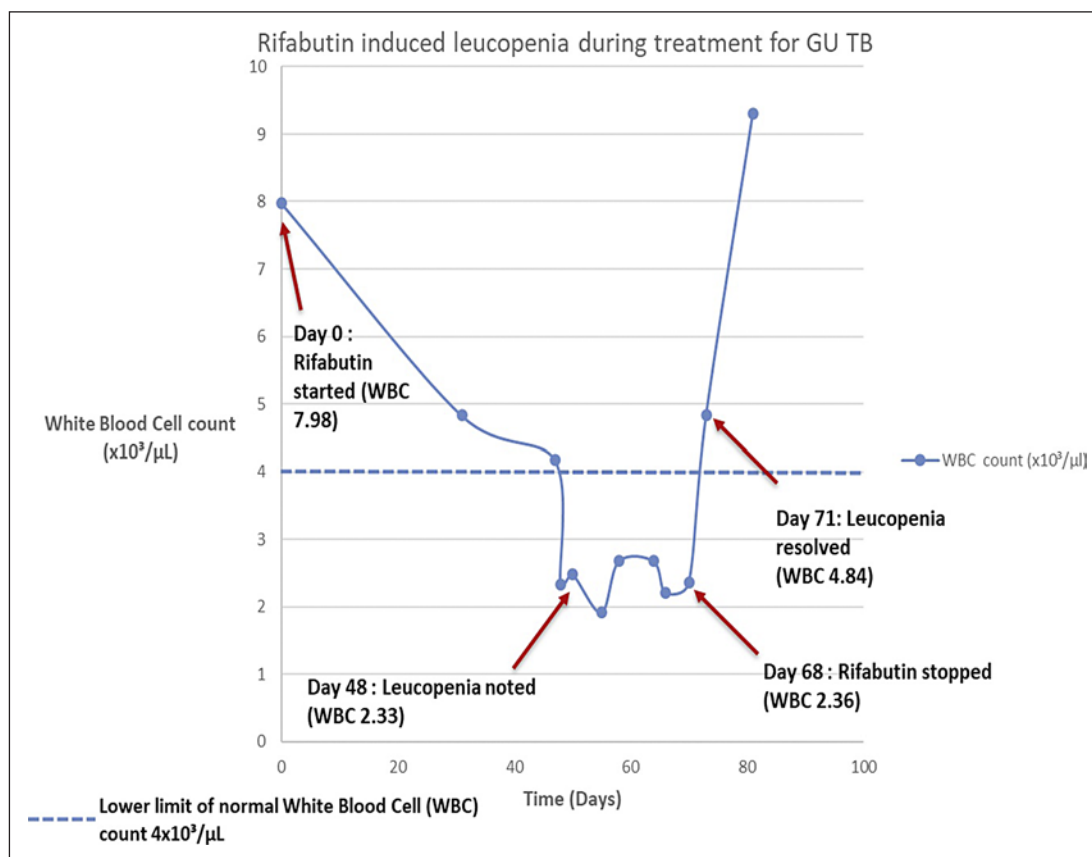


Fig. 2. Timeline of development and resolution of leucopenia in relation to the time of starting and stopping rifabutin treatment in genitourinary tract TB.

Rifampicin can reduce serum levels of both calcineurin inhibitors and corticosteroids through increased activity of cytochrome P-450 hepatic metabolism [6]. Difficulty maintaining therapeutic levels of immunosuppressants and episodes of graft rejection (33–35%) [3] while on rifampicin is well recognized [6]. Published guidelines recommend avoiding rifampicin or increasing immunosuppressant doses at least three to five folds during rifampicin use [6]. Our patient was on both tacrolimus and corticosteroids with rifabutin as part of initial TB treatment. Rifabutin is also a derivative of rifamycin S with the advantage of being a much weaker inducer of the cytochrome P-450 system compared to rifampicin [8]. A Cochrane review comparing the efficacy of both in treating pulmonary TB suggested equal efficacy in achieving cure and preventing relapse [7]. Information on the use of rifabutin for posttransplant TB is more limited, with successful outcomes reported from case reports and single-centre studies [8, 9].

Despite stopping rifabutin, hyponatremia persisted with urine that was not maximally dilute, suggesting persistent SIADH. TB infection can also induce hyponatremia through adrenal insufficiency but more commonly through SIADH secondary to active TB infection and TB medications. This raises the possibility that the SIADH may have also been associated with the patient's underlying tuberculosis. Although serum sodium improved with fluid restriction, which is the treatment for SIADH no matter the cause, drug-induced SIADH seems more likely as serum sodium, white cell count, and clinical symptoms improved with rifabutin cessation.

Rifabutin-induced SIADH appears idiosyncratic, with no plausible pharmacological explanation for this effect [10], while reports on whether rifabutin-induced leucopenia is dose

dependent are mixed [10]. Although both SIADH and leukopenia resolved after drug cessation, this does not indicate that the relationship is definite, but as our patient had no prior history of leukopenia and both SIADH and leukopenia resolved on drug cessation, we think it is more probable to be secondary to rifabutin.

There has been only one report of rifabutin-induced SIADH and leukopenia occurring in an immunocompetent patient treated for *Mycobacterium avium* complex infection [10]. In conclusion, this case is the first report of biochemically proven SIADH and leukopenia directly caused by rifabutin in the treatment of GU TB in a renal transplant recipient that fully reversed after switching rifabutin to rifampicin. Renal, transplant, and TB physicians managing TB with rifabutin following organ transplantation should be aware of this potential complication by closely monitoring serum sodium and white count during treatment. The importance of individualized care is also highlighted as switching to rifampicin enabled successful completion of TB treatment.

Statement of Ethics

Ethical approval was not required from Newcastle and North Tyneside Research Ethics Committee. This was in accordance with local and national guidelines with case studies such as this report being granted an exemption from requiring ethical approval. Written and verbal informed consent was obtained from the patient to publish their case history and images in the medical literature.

Conflict of Interest Statement

The authors have no conflicts of interest to declare that are relevant to the content of this article.

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Author Contributions

Material preparation, written informed consent, and data collection were performed by Maha Mohamed, a trainee in nephrology. The manuscript was written both by Maha Mohamed and Muhammad Waseem Athar, a trainee in respiratory medicine. Yaasir Mamoojee, Alison Brown, Frances Downen, and Jim Macfarlane commented on the previous versions of the manuscript and read and approved the final manuscript.

Data Availability Statement

Data from this report are included in this article. Further enquiries can be directed to the corresponding author.

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