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Recurrent neutropenia induced by rifabutin in a renal transplant recipient

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To the Editor,

Tuberculosis (TB) is one of the most common opportunistic infections and is associated with high morbidity and mortality. Rifampicin is an essential first-line anti-TB drug; however, it sometimes induces acute rejection by decreasing the blood levels of calcineurin inhibitors via the induction of cytochrome P450 in renal transplant recipients. Therefore, rifabutin, a weaker inducer of cytochrome P450 enzymes, is recommended as an alternative to rifampicin [1,2]. We report herein a case of rifabutin-related recurrent neutropenia in a renal transplant recipient.

A 48-year-old woman was admitted because of fever and increased urinary frequency. She had undergone two kidney transplantations: the first in 1989 and the second in 2012. No TB prophylaxis was performed during these two kidney transplantations. The patient was treated with tacrolimus (1 mg/day) and prednisolone (5 mg/day). Mycophenolic mofetil administration was stopped 2 months after the second transplantation because of gastrointestinal discomfort. The clinical course after the second transplantation was uneventful until a palpable mass was detected in her neck. She was diagnosed with TB lymphadenitis based on biopsy findings 14 months after the second

transplantation. One month before admission, TB treatment was initiated with a combination of isoniazid (300 mg/day), ethambutol (600 mg/day), and rifabutin (300 mg/day).

To maintain an appropriate serum concentration of tacrolimus, which is metabolized by cytochrome P450, we chose rifabutin instead of rifampicin because rifabutin has a weaker potency of cytochrome P450 induction than does rifampicin. Moreover, pyrazinamide, which can precipitate gout flares by decreasing renal excretion of uric acid, was not used because the patient was taking the uricosuric agent benzbromarone to treat persistent hyperuricemia.

On admission, the patient's complete blood count (CBC) showed a white blood cell (WBC) count of 2,200 cells/mm^3 and an absolute neutrophil count (ANC) of 1,780 cells/mm^3. Urinalysis revealed an increased leukocyte count and nitrite positivity, suggesting a urinary tract infection. Intravenous antibiotic therapy was initiated to treat the urinary tract infection. A CBC performed the next day revealed persistent neutropenia (ANC, 860 cells/mm^3); therefore, granulocyte colony-stimulating factor (G-CSF) was subcutaneously injected. Thereafter, the ANC recovered to the reference range and the patient was discharged after completion of a

5-day antibiotic treatment. Three weeks later, she was readmitted because of fever and urinary incontinence, symptoms suggestive of a recurrent urinary tract infection. To treat both the first and second urinary tract infections, we intravenously administered 1 g of meropenem every 8 hours, based on the previous urine culture in which extended-spectrum beta lactamase—producing *Escherichia coli* was found.

The next day, a sharp decrease in the WBC count (3,530 to 1,470 cells/mm³) and ANC (2,930 to 410 cells/mm³) occurred. On day 3, the patient's symptoms improved, and the urinalysis findings normalized; however, the WBC count and ANC remained low (1,460 and 650 cells/mm³, respectively). G-CSF was administered, and the ANC temporarily increased to 4,880 cells/mm³; however, it decreased to < 1,000 cells/mm³ 2 days later, as shown in Fig. 1.

The serum trough level of tacrolimus, which had remained stable at 8.0 to 10.0 ng/mL with 1 mg/day of tacrolimus after the transplantation, decreased gradually after administration of TB medication to 3.0 to 3.7 ng/mL. We assumed that the rifabutin had influenced this change. Because a second transplantation increases the risk of rejection, we did not taper the dose of tacrolimus, but instead increased it to 2 mg/day to achieve the target trough level. The serum creatinine level ranged from 0.74 to 1.02 mg/dL and showed little difference from before administration of the TB medication.

In the present case, the recurrent neutropenia tem-

porarily responded to G-CSF therapy. Recurrence of neutropenia despite amelioration of the urinary tract infection suggests that the drugs administered to the patient caused the neutropenia. Therefore, we reviewed the patient's medication and selected fexofenadine, meropenem, and rifabutin as the possible causative drugs. Fexofenadine was excluded after considering that the patient had taken this drug for several months before the development of neutropenia. Meropenem was also suspected; however, withdrawal of this drug did not improve the neutropenia. Therefore, rifabutin was suspected as the cause of neutropenia in the present case, and a review of the literature supports our presumption of a close association between rifabutin and neutropenia [3-5]. Our suspicion was confirmed by the replacement of rifabutin with levofloxacin. One week after switching to levofloxacin, the WBC count increased to 5,400 cells/mm³, and no further neutropenia was observed during the 6-month follow-up period (Fig. 1).

To date, rifabutin-induced neutropenia is not a well-known adverse effect, and it has only been described in case reports. However, in a multicenter study performed to evaluate the tolerance and potential pharmacokinetic interactions between azithromycin and rifabutin, the incidence of neutropenia ranged from 10% to 26%, and a significant decrease in the ANC was observed during the initial 14 days of monotherapy with rifabutin [5]. These findings suggest that rifabutin-induced neutropenia is not a rare event, and it is recommended that the WBC count be monitored for 1 week after the initiation of therapy and at 2- to 4-week intervals thereafter to avoid life-threatening neutropenia [3].

In summary, we have reported a case of neutropenia caused by rifabutin during the treatment of TB in a renal transplant recipient. Rifabutin-induced severe neutropenia can lead to serious consequences in renal transplant recipients. Hence, early and frequent monitoring of the hematologic profile is needed in patients receiving rifabutin during renal transplantation.

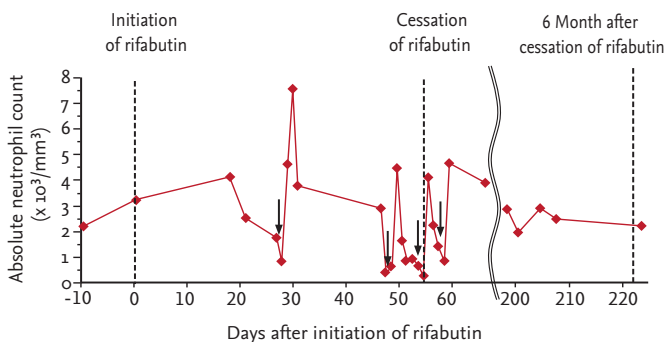**Keywords:** Rifabutin; Neutropenia; Kidney transplantation

Figure 1. Serial follow-up of absolute neutrophil count (ANC) during antituberculosis treatment. Note prompt improvement in ANC after changing from rifabutin to levofloxacin. The arrows indicate the timing of granulocyte colony-stimulating factor injection.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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