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CASE REPORT

Fever in a transplant recipient: think beyond infection

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Key Clinical Message

Immune reconstitution inflammatory syndrome (IRIS) is an exaggerated inflammatory cascade initiated in response to immune recovery during the resolution of an infection. Reduction in calcineurin inhibitor levels in organ transplant recipients due to enhanced metabolism from interaction with rifampin can predispose these individuals to develop IRIS during the treatment of tuberculosis and mimic sepsis.

Keywords

Drug interaction, immune reconstitution inflammatory syndrome, rifampin, tacrolimus, transplant

Introduction

Immune reconstitution inflammatory syndrome (IRIS) is an intense inflammatory response triggered by rapid recovery of immune system during the treatment of infection, which can lead to paradoxical deterioration in clinical status [1]. IRIS was originally described in HIV population during antiretroviral therapy. However, rarely IRIS can be seen in solid organ transplant recipients during the treatment of opportunistic infections including cryptococcosis, aspergillosis, candidiasis, histoplasmosis, polyomavirus nephropathy, and tuberculosis (TB), especially when the therapeutic immunosuppression is lowered [1–3]. As IRIS commonly presents with systemic inflammatory features such as fever and tachycardia, it can be misconstrued as sepsis. Herein, we report a unique case of IRIS in a non-HIV, immunocompromised liver-kidney transplant recipient being treated for TB, due to drug interaction between rifampin and tacrolimus.

Case Presentation

A 74-year-old Asian male with a history of orthotopic liver transplantation 4 years prior to presentation for hepatitis C cirrhosis and deceased donor kidney transplant a year prior to presentation for end-stage renal disease secondary to calcineurin inhibitor (CNI) toxicity was transferred to our institution for the management of disseminated tuberculosis. Patient was on RIPE (rifampin, isoniazid, pyrazinamide, ethambutol) therapy for TB initiated at the originating hospital about a week prior to presentation. He was on triple antirejection therapy with tacrolimus 4 mg twice a day, mycophenolate mofetil 1000 mg twice a day, and prednisone 5 mg per day. Serum tacrolimus level was undetectable on presentation likely due to its accelerated metabolism from interaction with rifampin. Soon after admission, he developed fever up to 104.4°F, tachycardia, tachypnea, and mild hypotension. There were no localizing findings or imaging evidence suggestive of infectious source. Renal function was preserved. C-reactive protein (CRP) was markedly elevated. He was started on broad-spectrum antibiotics after obtaining cultures for the treatment of presumed sepsis. Serology for CMV, Histoplasma, and Cryptococcus as well as blood and urine cultures were negative; hence, antibiotics were discontinued. He was suspected to have developed IRIS; intravenous methylprednisolone therapy was initiated, and tacrolimus dose was adjusted to achieve therapeutic plasma concentration (5–7 ng/mL). Patient improved clinically with symptom resolution over the next 2 days. CRP down trended rapidly.

Discussion

With the increasing use immunosuppressive and immunomodulatory agents with potent effects on the immune system in transplant patients, it is important for general physicians caring for these patients to be familiar with these agents and their potential interactions. Timely recognition and appropriate treatment of IRIS is critical for the prevention of severe complications including allograft loss [3]. IRIS is primarily mediated through increased activation of T-helper cell (Th) response, leading to improvement in immunity. On the other hand, CNIs such as tacrolimus act by decreasing T-cell activation. Hence, rapid reduction in immunosuppressive drug levels can predispose these individuals to the development of IRIS through a relative increase in Th1 cell response [1]. Clinically, IRIS is a diagnosis of exclusion and can present with wide array of clinical features, which can be organ specific (worsening pleural effusion, lymphadenopathy, pericardial effusion or appearance of new pulmonary lesions) or systemic inflammatory features (fever, tachycardia), mimicking either a new infection or paradoxical worsening of a preexisting infection. Several drugs including rifampin, *artemether*/lumefantrine, naffcillin, and efavirenz induce CYP3A4 and P-glycoprotein in the liver and small bowel leading to increased metabolism of CNIs [4] and hence increase the risk for development of IRIS in transplant patients being treated for various infections. Moreover, this can also predispose to allograft rejection. While recovery from tuberculosis infection itself has been recognized as a risk factor for IRIS, it is expected to occur ~56 to 87 days after initiation of antituberculous therapy [5]. Based on the temporal profile and prompt clinical response to increased tacrolimus levels, we believe that our patient developed IRIS secondary to immune system reactivation from resolving infection with reduced tacrolimus levels from interaction with rifampin. It is important to monitor CNI levels regularly in hospitalized transplant patients, particularly in those receiving antimicrobial therapy, so that any aberrations could be addressed promptly.

Informed Consent

Informed consent has been obtained for the publication of this case report.

Conflict of Interest

The authors have declared that no conflict of interest exists.

Authorship

All the authors made substantial contribution to the preparation of this manuscript and approved the final version for submission. MK: drafted the manuscript; VC: procured the necessary clinical information; AK and AHS: reviewed and revised the manuscript for critically important intellectual content.

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