TRANSPLANT INTERNATIONAL

Transplant International ISSN 0934-0874

CASE REPORT

Fever and pneumonitis induced by enteric-coated mycophenolate sodium in a patient after kidney transplantation

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Keywords
drug-induced fever, mycophenolate, neutrophil granulocytes, pneumonitis.

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Conflict of interest
None.

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Received: 30 December 2012
Revision requested: 6 February 2013
Accepted: 20 March 2013
Published online: 17 April 2013

doi:10.1111/tri.12104

Summary

Here, we report on a patient after kidney transplantation, who developed fever and pneumonitis due to mycophenolic acid (MPA) treatment. Decreasing MPA dosages improved the symptoms, but after rechallenge with higher MPA doses the symptoms recurred. Discontinuation of MPA resulted in a complete resolution of fever within 24 h and a rapid improvement in pneumonitis. *In vitro*, the patient's polymorphonuclear neutrophils (PMNs) developed increased oxidative burst when incubated with MPA and N-formyl Met-Leu-Phe. We first report on MPA-induced pneumonitis and show that MPA can induce a pro-inflammatory response in kidney-transplanted patients. These pro-inflammatory changes might be due to paradoxical activation of PMNs.

Mycophenolic acid (MPA) is part of current immunosuppressive regimens in kidney transplantation (1,2). The major, dose-dependent side effects of MPA – CMV infections, leucopenia and gastrointestinal symptoms – are equally well-described as its clinical efficacy in reducing acute rejection rates and graft loss. Within the past years, few reports were published on pro-inflammatory effects of MPA (3–5). They described patients with granulomatosis and polyangiitis, rheumatoid arthritis or renal transplant recipients who presented with fever, arthralgias, oligoarthritis and elevated C-reactive protein (CRP) levels due to MPA treatment (3–5). Two reports suggested a pro-inflammatory reaction of the innate immune system shown by either increased IL-6 serum levels or PMN activation (4,5).

Case report

On 19 September 2012, a patient, who received a kidney transplant in April 2012 because of autosomal-dominant polycystic kidney disease, was admitted because of fever up to 39°C. The patient received an immunosuppressive treatment regimen with cyclosporine A (trough levels 100–120 ng/ml), 5 mg of aprednisolon and enteric-coated MPA 720 mg daily. Concomitant medication consisted of carvedilol, rilmenidin, amlodipine, valsartan and

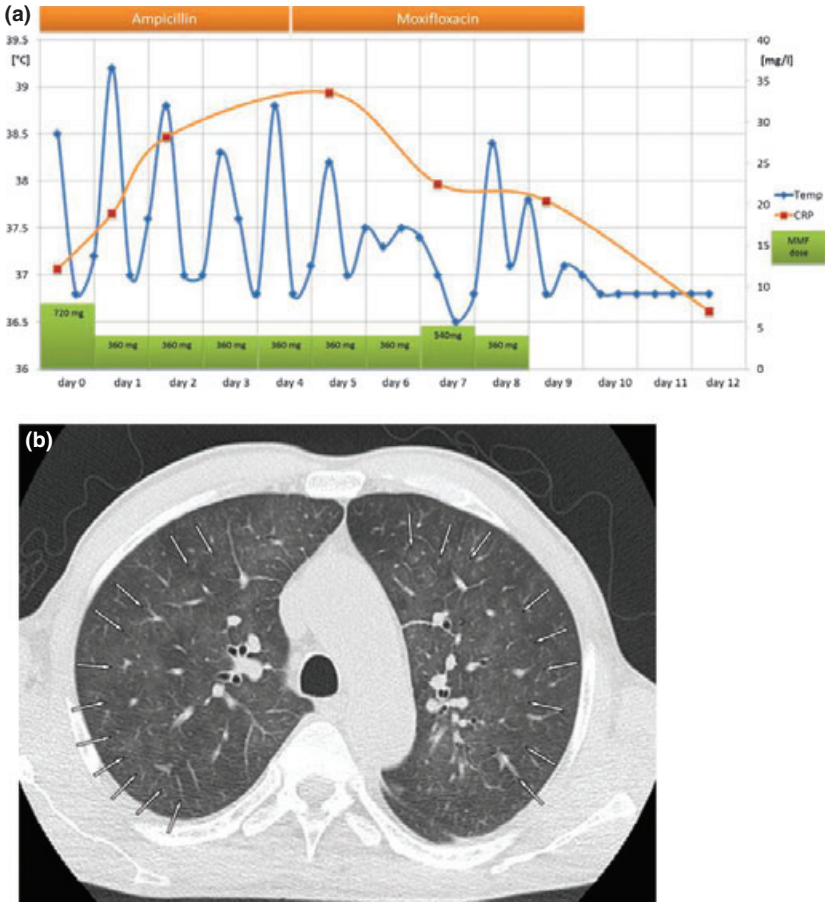

Figure 1 Clinical parameters and CT scan. (a) The course of fever, CRP levels, mycophenolic acid dose and antibiotic treatment during the hospital stay are shown. (b) Representative computed tomography of the chest, axial orientation, 64 slice-CT scanner (slice thickness 3 mm, collimation 2.4 mm). In the lung window, areas of ground glass opacity were found in the central areas of both lungs (arrows), sparing the peripheral lung parts. These are specific signs for usual interstitial pneumonia, which may occur in some cases under immunosuppressive therapy.

hydrochlorothiazide because of hypertension. Furthermore, he was treated with valganciclovir because of CMV infection in July 2012.

After transplantation, the patient was treated with MPA 1440 mg daily and received high dosage aprednisolon in post-transplantation phase. Two months after kidney transplantation, MPA was stopped because of CMV infection. One month later, upon negative CMV PCR, MPA was restarted in a decreased dosage (max. 360 mg daily). In August 2012, he was administered a corticosteroid bolus treatment because of biopsy-proven BANFF 1a rejection and MPA was increased to 720 mg daily. The above-described complaints started when the MPA dose was 720 mg and aprednisolon was tapered to 5 mg.

Fever was accompanied by malaise, mild arthralgias and nonproductive cough. Chest X-ray revealed discrete signs of peribronchitis. Serial urine and blood cultures remained negative. Laboratory evaluations showed leucocyte counts of 4000/μl, CRP levels of 33 mg/l and a procalcitonin level of 0.17 ng/ml. Initially, viral infection or infection with atypical bacteria was suspected, but PCR for detection of CMV, EBV and BK virus in the blood were negative. Testing for atypical bacteria remained negative (Legionella antigen, Legionella IgM/IgG titres, *Chlamydia pneumoniae/trachomatis* IgA, *Mycoplasma pneumoniae*). In line, PCR for the detection of *C. pneumoniae*, Legionella and *M. pneumoniae*, as well as respiratory syncytial virus in the sputum of our patient, was negative. Furthermore, serology for adenovirus, coxsackie A/B virus, influenza A/B virus, parainfluenza virus type 1, 2 and 3 as well as parvovirus B19 IgM revealed negative results. The nasal swab for the detection of influenza and parainfluenza virus via PCR was negative.

The patient was first treated with ampicillin while MPA was reduced to 360 mg b.i.d., but fever remained high and CRP levels unchanged. Thus, we changed the antibiotic regimen to moxifloxacin treatment and further reduced MPA to 180 mg b.i.d. This combination resulted in subfebrile temperatures, but the pulmonary complaints remained

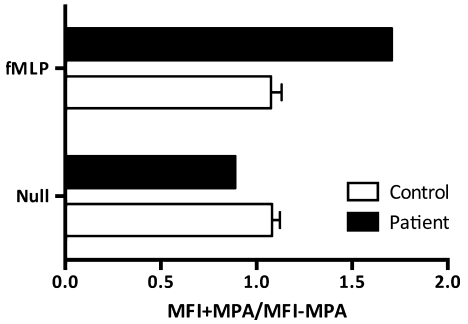

Figure 2 Oxidative burst in polymorphonuclear neutrophils (PMNs). PMNs of the patient (black column) and the controls (white column; $n = 5$) were not stimulated (null) or 10^{-6}M fMLP with or without 2 μg/ml mycophenolic acid (MPA) for 30 min at 37°C. The fold increase in reactive oxygen species in PMNs treated with MPA is shown in relation to the oxidative burst treated without MPA and the respective stimulus.

(Fig. 1a). Therefore, a CT scan of the chest, which showed interstitial pneumonitis, was performed (Fig. 1b). Because of the improvement of fever, we again increased the MPA dose to 540 mg daily under continuation of moxifloxacin treatment. Immediately, the patient developed fever up to 38.5°C (Fig. 1a). Because of a suspected inflammatory syndrome caused by MPA treatment, we decided to discontinue MPA and change immunosuppression to azathioprine. Within 12 h the fever resolved, CRP levels dropped to normal values and the pulmonary complaints improved rapidly.

In vitro data

Previous reports suggest that MPA can activate the innate immune system (4,5). Thus, we evaluated PMNs in the above-described patient compared with five healthy controls. PMNs were isolated from the patient and five healthy controls. We evaluated the intracellular oxidative burst after stimulation with 1 μM N-formyl Met-Leu-Phe (fMLP) after 30 min incubation at 37°C and 5% CO_2 with or without 2 μg/ml MPA (all from Sigma, St. Louis, MO, USA). Reactive oxygen species (ROS) were detected with 2, 7-dichlorofluorescein diacetate as previously described (6). The mean fluorescence intensity (MFI) of PMNs treated with MPA was compared with the MFI of the respective stimulus without MPA. Interestingly, there was no difference in the oxidative burst between the two individuals with or without MPA when no stimulus was added. However, when the patient's PMNs were stimulated with fMLP in the presence of MPA, ROS-production increased by 1.7-fold. In contrast, there was no difference in the stimulated healthy control PMNs with or without MPA (Fig. 2). In summary, we propose that the patient's PMNs reacted to MPA in the presence of an additional stimulus.

Discussion

Here, we provide first evidence of a kidney-transplanted patient, who presented with pneumonitis and high fever because of pharmacotherapy with enteric-coated MPA. MPA has already been described to induce inflammatory syndromes in patients with either autoimmune diseases such as granulomatosis with polyangiitis and rheumatoid arthritis (3,4) or kidney transplantation (5). Interestingly, our described patient developed the observed MPA side effect 5 months after starting MPA treatment. We propose two explanations for the relatively late onset of complaints. Firstly, the patient received high dose corticosteroids in the immediate post-transplant phase because of BANFF1a rejection. Intermittently MPA treatment had to be stopped because of CMV infection. Fever and pneumonitis occurred when the corticosteroid dose was tapered to 5 mg and MPA dosage was 720 mg. Thus, corticosteroid therapy might have masked the side effect of MPA. Furthermore, the observed side effect seems to be strongly dependent on the MPA dosage, which is confirmed by the fact that increasing the dose led to an immediate aggravation of complaints. This is consistent with a previous report on the reappearance of an inflammatory syndrome after rechallenging a patient with MPA (4). Secondly, a viral or bacterial infection – not detected by the performed tests – may have triggered the paradoxical reaction in PMNs. This is supported by the fact that the patient's PMNs developed increased ROS-production in the presence of MPA only when restimulated.

A limitation of our study is the fact that respiratory virus infection cannot be totally excluded as cause of complaints as broncho-alveolar lavage was not performed. Nevertheless, increasing the MPA dosage immediately resulted in reappearance during the hospital stay, which strongly supports our diagnosis of MPA-induced inflammatory syndrome.

Contrary to previous reports, the patient presented with mild arthralgias rather than impressive oligoarthritis (3–5). Also, measured CRP values were significantly lower than reported before (3–5). To date, we can only speculate on the causes of the different clinical pictures of MPA-induced inflammatory syndrome, e.g. concomitant medication with corticosteroids or infection. Consistent with our previous report (5), procalcitonin remained negative in our patient. We here provide additional evidence to show that procalcitonin is an important marker for discriminating bacterial infections and other noninfectious causes of elevated CRP, such as drug fever (7,8).

Our report adds to the increasing evidence that MPA can induce pro-inflammatory effects in patients receiving the drug as immunosuppressant in kidney transplantation. Even though MPA-induced inflammatory syndrome is a

rare side effect, it is of utmost importance for treating our patients with kidney transplantation and should be kept in mind as differential diagnosis in transplant patients with fever of unknown origin. Nevertheless, further studies are needed to evaluate the exact mechanisms of this paradoxical reaction to develop strategies to adapt our patients' pharmacotherapy.

Authorship

MP: treated the patient, analysed the data and wrote the manuscript. AK: performed the research and wrote the manuscript. EH: performed the research (CT scan). AR: analysed the data and wrote the manuscript. KE: treated the patient, analysed the data, performed the research and wrote the manuscript.

Funding

None.

References

1. Sievers TM, Rossi SJ, Ghobrial RM, *et al.* Mycophenolate mofetil. *Pharmacotherapy* 1997; **17**: 1178.
2. Allison AC, Eugui EM. Mycophenolate mofetil and its mechanisms of action. *Immunopharmacology* 2000; **47**: 85.
3. Loock J, Lamprecht P, Gross WL. Acute inflammatory syndrome with elevated procalcitonin induced by mycophenolate sodium. *J Rheumatol* 2012; **39**: 658.
4. Maes B, Oellerich M, Ceuppens JL, *et al.* A new acute inflammatory syndrome related to the introduction of mycophenolate mofetil in patients with Wegener's granulomatosis. *Nephrol Dial Transplant* 2002; **17**: 923.
5. Hochegger K, Gruber J, Lhotta K. Acute inflammatory syndrome induced by mycophenolate mofetil in a patient following kidney transplantation. *Am J Transplant* 2006; **6**: 852.
6. Rosenkranz AR, Templ E, Traindl O, Heinzl H, Zlabinger GJ. Reactive oxygen product formation by human neutrophils as an early marker for biocompatibility of dialysis membranes. *Clin Exp Immunol* 1994; **98**: 300.
7. Simon L, Gauvin F, Amre DK, Saint-Louis P, Lacroix J. Serum procalcitonin and C-reactive protein levels as markers of bacterial infection: a systematic review and meta-analysis. *Clin Infect Dis* 2004; **39**: 206.
8. Eberhard OK, Haubitz M, Brunkhorst FM, Kliem V, Koch KM, Brunkhorst R. Usefulness of procalcitonin for differentiation between activity of systemic autoimmune disease (systemic lupus erythematosus/systemic antineutrophil cytoplasmic antibody-associated vasculitis) and invasive bacterial infection. *Arthritis Rheum* 1997; **40**: 1250.