CASE REPORT

Systemic inflammatory response in a liver transplant recipient: a potential side effect of mycophenolate mofetil

Rebecca Smith,¹ Adam Testro^{1,2}

¹Liver Transplant Unit Victoria, Austin Health, Australia
²Department of Medicine, University of Melbourne, Melbourne, Australia

Correspondence to

Dr Rebecca Smith,
 rebeccasmith212@gmail.com

Accepted 6 March 2018

SUMMARY

Mycophenolate mofetil is a commonly used immunosuppressive medication in the postliver transplant setting where gastrointestinal side effects tend to predominate. However, in more recent times, emerging and rare side effects are being reported in the literature. We present a case of a patient who had a significant inflammatory response and associated marked weight loss with the up-titration in dose of mycophenolate mofetil. Extensive investigations were performed to exclude other infective, inflammatory or malignant aetiologies for these symptoms, however no other cause was identified. The patient had the medication ceased and subsequently had a dramatic improvement in his inflammatory markers and regained the weight lost while on the medication.

BACKGROUND

Liver transplantation requires a combination of immunosuppression to prevent allograft rejection. At our centre, a combination of glucocorticoids, calcineurin inhibitors and antimetabolite medications are commonly used. Mycophenolate mofetil (MMF) is an antimetabolite, and the mechanism of action is through the conversion to mycophenolic acid which inhibits purine synthesis, resulting in an antiproliferative effect on T and B lymphocytes.¹ MMF is usually well tolerated, however gastrointestinal side effects predominate. It is a suitable immunosuppressive agent in patients who require a calcineurin inhibitor sparing regimen, such as those with impaired renal function or features of the metabolic syndrome. MMF is becoming more commonly used in modern-day transplantation, and thus, more unusual side effects are being reported.

CASE PRESENTATION

A 67-year-old man was admitted to hospital for investigation of an 8-month history of feeling generally unwell with associated night sweats and a 10 kg weight loss on a background of a liver transplant 2 years and 9 months prior for cryptogenic cirrhosis. Other symptoms associated with the presentation included a long-standing cough with occasional white sputum production which was under investigation of the respiratory department. The patient had some minor joint pain affecting both hands and knees on the background of known rheumatoid

arthritis. Of note, the patient denied rigors, lymphadenopathy, other localising symptoms of infection and no travel overseas since transplantation. There was no history of alcohol use, smoking, illicit drug use and no exposure to animals or sick contacts.

The patient was not on any treatment for rheumatoid arthritis apart from prednisolone in the post-transplant setting. Other medical history for this patient included type 2 diabetes mellitus, chronic kidney disease, hypertension, atrial fibrillation and osteoarthritis. Immunosuppression medication included tacrolimus 1 mg in the morning and 0.5 mg at night, MMF 1000 mg twice daily, prednisolone 5 mg daily.

The history of MMF dosing was that immediately post-transplant, it was started at 1000 mg twice daily for 3 months until neutropenia resulted, and the medication was ceased. Over a year after the cessation, when the neutropenia resolved and in the setting of a planned reduction of tacrolimus in the setting of chronic kidney disease, MMF was reintroduced at 500 mg twice daily for 4 months until the dose was increased again to 1000 mg twice daily. The onset of the symptoms experienced by the patient coincided with the reintroduction of MMF 1000 mg twice daily.

The patient underwent oral, lymphnode, cardiovascular and respiratory examinations that were all unremarkable. Abdominal examination revealed a L-shaped scar from prior liver transplant but no organomegaly or tenderness. The recorded weight on admission was 81 kg with a body mass index (BMI) of 28.4. His baseline weight was 92 kg with a BMI of 32.2. There were no documented fevers during the hospital admission.

INVESTIGATIONS

Blood tests revealed elevated inflammatory markers with erythrocyte sedimentation rate (ESR) at 118 mm/hour and C reactive protein (CRP) 138 mg/L as the highest recorded results. Full blood count, renal function and liver function tests were similar to the patient's baseline tests. It was noted that the patient had long-standing hypoalbuminaemia at 27 g/L and anaemia with a haemoglobin of 10.4 g/dL. A myeloma screen, flow cytometry, QuantiFERON Gold, HIV and multiple series of blood cultures were all unremarkable. The rheumatological investigations revealed positive antinuclear antibodies (ANA)

To cite: Smith R, Testro A. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2017-223767

with a titre of 1:80, positive rheumatoid factor with a titre of 109 and a positive anti-cyclic citrullinated peptide (anti-CCP) with a titre of 147. These findings were in keeping with the known diagnosis of rheumatoid arthritis. Anti-neutrophil cytoplasmic antibodies (ANCA) was positive, however specific tests for myeloperoxidase (MPO) and proteinase 3 (PR3) were negative and a full Anti-Extractable nuclear antigens (anti-ENA) panel was negative. Cytomegalovirus and Epstein-Barr virus PCR were negative, and toxoplasmosis and Q fever serology were also negative.

Two CT chest, abdomen and pelvis were performed. The first completed at the time of onset of symptoms 8 months prior and the second on admission to hospital. Imaging revealed small mediastinal and hilar lymphadenopathy without change in size across an 8-month period, with a maximal diameter of 10 mm. A transthoracic echocardiogram was performed which demonstrated no valvular lesions and a normal left ventricular function. A bronchoscopy was performed given the initial symptom of cough, however this was a normal examination. Furthermore, a positron emission tomography scan was performed which demonstrated fluorodeoxyglucose (FDG)-avid mediastinal lymphadenopathy. Given the FDG avidity of these lesions, the patient underwent a second bronchoscopy for further washings and endobronchial ultrasound and biopsy of the lymphadenopathy. Bronchial washings were again normal, and flow cytometry of the biopsied tissue was also normal and did not demonstrate any evidence of a lymphoproliferative disorder.

DIFFERENTIAL DIAGNOSIS

Treatment

During the inpatient admission, the decision was made to reduce the MMF from 1000 mg twice daily to 500 mg twice daily. Three days following on from the medication change, the CRP fell

from 106 to 14. The CRP prior to this change had consistently remained greater than 100 for at least 2 months prior to the medication change. The patient also improved significantly from a symptomatic perspective and the night sweats abated. Empiric antibiotics were not given to the patient in hospital.

Outcome and follow-up

MMF was ceased in the outpatient clinic 2 weeks after discharge, and the patient has been followed up continually and remains well. Two weeks after the cessation of the MMF in the clinic, the CRP continued to fall to 5 and the ESR fell to 30. This likely remains slightly elevated in the setting of ongoing untreated rheumatoid arthritis. A further 6 months after the cessation of MMF, the patient has returned to his baseline weight (figure 1). At this time point, the patient also has an improved albumin at 32 and normal haemoglobin at 141.

DISCUSSION

MMF has been more commonly prescribed as part of an immunosuppressive regimen in liver transplant recipients since studies demonstrated an improvement in graft and patient survival.² MMF has the benefit of having significant metabolic and renal benefits compared with tacrolimus, however this does not come without the drug's own set of side effects.³ The most common side effect seen with the use of MMF is that of disturbances of the gastrointestinal system with nausea, vomiting, diarrhoea and abdominal pain occurring in up to 45% of patients which often results in medication cessation or dose reduction.⁴ This is most likely related to the active immunosuppressive product of MMF, mycophenolic acid, being located preferably in the epithelial cells of the gastrointestinal tract and that enterocytes are dependent on the de novo purine synthesis pathway which is the target

Figure 1 Weight and C reactive protein (CRP) changes in response to mycophenolate dosing changes.

of inhibition and method of action of mycophenolic acid.⁴ Other common negative side effects that are more prominent with MMF compared with tacrolimus include haematological side effects such as leucopenia and thrombocytopenia, and there is also evidence to suggest an increased risk of opportunistic infections and cytomegalovirus infection compared with some other commonly used immunosuppressants.^{3 5} Furthermore, there are significant teratogenic effects of MMF, and it is therefore not advised in pregnancy.⁶ Gastrointestinal bleeding has also been reported in a small number of studies.

As MMF becomes more commonly used as part of post-transplantation immunosuppression and as a therapy in a number of other autoimmune conditions, more side effects of the medication are beginning to emerge. In the literature to date, there have been a number of interesting case reports including MMF-induced myopathy in a patient requiring treatment of lupus nephritis which resolved with the cessation of therapy and pulmonary toxicity presenting as pneumonitis in a patient treated with MMF postrenal transplant.^{7 8} There has only been one other case report in the literature demonstrating a drug fever attributed to MMF in a renal transplant recipient, and this was not associated with elevated inflammatory markers as seen in our patient's condition.⁹ In this case report, there was a strong temporal relationship with the cessation of the medication and the resolution of fever, and similarly in our patient with the cessation of MMF the inflammatory markers fell dramatically and the symptoms experienced also improved. This is the first reported case of a patient with

elevated inflammatory markers and significant weight loss as a probable side effect of MMF which resolved with the cessation of the medication.

Contributors RS: responsible for providing the medical care and coordinating the investigations for the patient in the hospital and reviewing the patients history. As part of the case report, this author was able to explore the medical history first-hand with the patient and by reviewing the prior medical records. This author is responsible for writing the case report. This author also completed an extensive review of the literature to determine if similar side effects or other rare case reports of unusual side effects secondary to mycophenolate mofetil had been published. This author reported to AT as the senior clinician involved in the case. AT: responsible for supervising the medical care of the patient quoted in the case report. This author was also responsible for following up the patient in the outpatient setting to ensure that the response after cessation of the medication was continued. This author also provided a contribution by reviewing the drafts and finalised case report for submission and ensured all the documentation was accurate prior to submission. The two authors collaborated and reviewed the project regularly to ensure all the information was accurate prior to submission.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

© BMJ Publishing Group Ltd (unless otherwise stated in the text of the article) 2018. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

REFERENCES

- Hood KA, Zarembski DG. Mycophenolate mofetil: a unique immunosuppressive agent. *Am J Health Syst Pharm* 1997;54:285–94.
- Wiesner RH, Shorr JS, Steffen BJ, *et al*. Mycophenolate mofetil combination therapy improves long-term outcomes after liver transplantation in patients with and without hepatitis C. *Liver Transpl* 2005;11:750–9.
- Boudjema K, Camus C, Saliba F, *et al*. Reduced-dose tacrolimus with mycophenolate mofetil vs. standard-dose tacrolimus in liver transplantation: a randomized study. *Am J Transplant* 2011;11:965–76.
- Behrend M. Adverse gastrointestinal effects of mycophenolate mofetil: aetiology. *Drug Saf* 2001;24:645–63.
- Pourfarziani V, Panahi Y, Assari S, *et al*. Changing treatment protocol from azathioprine to mycophenolate mofetil: decrease in renal dysfunction, increase in infections. *Transplant Proc* 2007;39:1237–40.
- Anderka MT, Lin AE, Abuelo DN, *et al*. Reviewing the evidence for mycophenolate mofetil as a new teratogen: case report and review of the literature. *Am J Med Genet A* 2009;149A:1241–8.
- Galindo M, Cabello A, Joven B, *et al*. Mycophenolate mofetil induced myopathy in a patient with lupus nephritis. *J Rheumatol* 2005;32:188–90.
- Shrestha NK, Mossad SB, Braun W. Pneumonitis associated with the use of mycophenolate mofetil, Transplantation. 2003;27:1762.
- Chueh S-C, Hong J-C, Huang C-Y, *et al*. Drug fever caused by mycophenolate mofetil in a renal transplant recipient—a case report. *Transplant Proc* 2000;32:1925–6.

Learning points

- Liver transplant patients are required to be on long-term immunosuppressive therapy and therefore are exposed to a number of side effects and complications of treatment.
- Mycophenolate mofetil is commonly used in the post-transplant setting due to its perceived 'safer' side-effect profile.
- Mycophenolate mofetil has an emerging side-effect profile.
- Mycophenolate mofetil reduction or cessation should be considered in patients with evidence of a systemic inflammatory response once the standard infectious and inflammatory screen has been completed.

Copyright 2018 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.

BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- Submit as many cases as you like
- Enjoy fast sympathetic peer review and rapid publication of accepted articles
- Access all the published articles
- Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow