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CASE REPORT

Acute Inflammatory Syndrome Following Introduction of Mycophenolate Mofetil in a Patient With Systemic Lupus Erythematosus

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Introduction

Mycophenolate mofetil (MMF) is an immunosuppressant that has been widely used in solid organ transplantation to prevent graft rejection in patients after kidney, liver, or heart transplants. Its active ingredient, mycophenolic acid, reversibly inhibits IMP dehydrogenase, a lymphocyte-specific enzyme, and therefore inhibits both T and B lymphocyte proliferation (1). MMF use is becoming more accepted as a treatment for various autoimmune disorders. It has been used as therapy for antineutrophil cytoplasmic antibody–associated vasculitis, inflammatory myopathy (2), and systemic lupus erythematosus (SLE) (1,3).

SLE is the one connective tissue disorder for which MMF use is currently most widely accepted. Initial broad use of MMF in lupus was prompted by a favorable study from Hong Kong that compared the use of MMF with standard therapy with cyclophosphamide (CYC) for diffuse proliferative lupus glomerulonephritis (World Health Organization [WHO] class IV) and found that patients treated with MMF have similar remission induction rates to the CYC-treated group (3) with fewer complications. Currently, MMF is used for various lupus manifestations including hematologic, cutaneous, and general disease activity (4,5).

In addition to clinical effectiveness, MMF use is also fostered by its favorable tolerability profile, with main side effects being nausea, diarrhea, headache, and less frequently, leukopenia. Acute inflammatory syndrome, an unusual complication of MMF therapy, has previously been reported in 2 patients with Wegener's granulomatosis (6) and in 1 patient following kidney transplantation (7). This syndrome was first described and named by Maes et al in 2002 (6). All 3 patients described previously developed arthritis, fever, and elevated inflammatory markers shortly after the introduction of MMF.

Here we report a patient with SLE who developed acute inflammatory syndrome after initiation of MMF and upon subsequent rechallenge with the medication. To our knowledge this is the first reported case of MMF-induced acute inflammatory syndrome in a patient with lupus.

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Dr. Cronin has received consultant fees (less than $10,000) from Medimmune and owns stock in Procter & Gamble.

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Case Report

The patient, a 36-year-old woman, has been treated in the rheumatology department at our institution since August 2005. She initially presented with fevers, abdominal pain, and pancytopenia as an inpatient transfer to our tertiary care center from an outside hospital. The patient had a medical history significant for primary biliary cirrhosis, antiphospholipid antibody syndrome, and immune thrombocytopenia. She was diagnosed with SLE during the summer of 2005 based on positive high-titer antinuclear antibodies >10 units/ml (normal range 0–1.4), positive anti-Sm antibodies at 629 units/ml (normal range 0–99), positive anti–double-stranded DNA (anti-dsDNA) antibodies at a titer of 1:1,280, and low C3 of 10 mg/dl (normal range 79–152) and C4 of <8 mg/dl (normal range 16–38). Her antiphospholipid antibody panel was positive for an elevated titer of IgG at 29 GPL (IgG phospholipid units/ml) (normal range 0–9) and IgM at 39 MPL (IgM phospholipid units/ml) (normal range 0–10). β_2-glycoprotein antibody and lupus anticoagulant were negative. The patient had a positive antimitochondrial antibody and a negative anti-smooth muscle antibody.

The patient had undergone a renal biopsy due to significant proteinuria of 5,788 mg/24-hour urine and the presence of red blood cell casts. The results were consistent with diffuse proliferative glomerulonephritis of lupus erythematosus (WHO class IV). Her other SLE manifestations included pulmonary hypertension with an estimated systolic pulmonary artery pressure of 72 mm Hg on echocardiogram, fatigue, and polyserositis.

Upon transfer to our institution, the patient was treated with intravenous (IV) methylprednisolone (1,000 mg/day for 3 days) and then switched to prednisone (60 mg/day).

She received IV CYC infusions 1,000 mg monthly for 6 months, while prednisone was successfully tapered to 30 mg/day. After successful completion of 6 months of IV CYC therapy and achieving disease remission in February 2006 she began taking MMF, which was chosen as a steroid-sparing and remission-maintaining agent. The patient was initially started on 500 mg once daily and the dosage was gradually titrated up to 1,000 mg twice daily over the next 2 months.

The patient was rehospitalized with subjective fevers and arthralgias involving her ankles, knees, wrists, and shoulders in May 2006, 1 month after increasing her MMF dosage to 2,000 mg/day. She developed the above symptoms several days after increasing the dosage of her medication from 1,000 mg/day to 2,000 mg/day. Upon admission, the patient's oral temperature was 99.9°F. On physical examination she had synovitis of her wrists, knees, and ankles. The patient had an elevated erythrocyte sedimentation rate (ESR) of 114 mm/hour (normal range 0–20), C3 of 81 mg/dl (normal range 79–152), C4 of 10 mg/dl (normal range 16–38), a negative antistreptolysin O titer, a mildly elevated white blood cell (WBC) count of 11,300/μl (normal range 4,000–10,000), normal liver function test findings, creatinine phosphokinase of 13 units/liter (normal range 24–180), normal chest radiographs, and negative urine culture. Urinalysis had 0–2 red blood cells, 0–2 WBCs, 3+ protein, and trace blood. Left knee arthrocentesis was performed, which revealed mildly inflammatory fluid with a WBC count of 2,800/μl with 18% polymorphonuclear cells, 3% lymphocytes, 10% monocytes, 69% macrophages, and no crystals on polarized microscopy.

The patient's presentation was initially thought to be consistent with SLE exacerbation based on elevated ESR, inflammatory arthritis, and lack of alternative explanation for her symptoms. MMF was discontinued. She was treated with IV methylprednisolone for 3 days and then switched to prednisone 60 mg/day. She was restarted on CYC at 1,300-mg monthly infusions, which she continued receiving for 4 additional months. The patient's arthritis was resolved the day after initiation of high-dose steroid treatment and prednisone was successfully titrated down to 20 mg/day.

The patient's condition stabilized rapidly, so after the 4 months of IV CYC, she restarted MMF as maintenance therapy. This time she was started on 1,000 mg twice daily, because it was thought that the gradual introduction of the medication previously may have contributed to her prior flare. The patient developed arthralgias, fatigue, and fevers 2 days after restarting MMF. Upon presentation her oral temperature was 99.0°F. On physical examination the patient had synovitis of her wrists, left elbow, and right ankle. Infectious evaluation was negative. Her serum WBC count was mildly elevated at 11,300/μl (normal range 4,000–10,000), C3 was 89 mg/dl (normal range 79–152), C4 was 16 mg/dl (normal range 16–38), anti-dsDNA assay was negative, creatinine phosphokinase was <10 units/liter (normal range 24–180), and ESR was 56 mm/hour (normal range 0–20).

MMF was discontinued permanently because it appeared that there was clearly a direct correlation between its use and the appearance of inflammatory symptoms. Calculated Naranjo algorithm score, which assesses the likelihood that a change in clinical status is the result of an adverse drug reaction rather than progression of the disease, was 11 (8). This makes an adverse drug reaction very likely in our patient, because a score >9 is consistent with a highly probable association. The patient's symptoms resolved within 3 days after discontinuation of the medication without any other therapy. She subsequently started receiving azathioprine and tolerated this medication well without recurrence of symptoms over the ensuing 10 months.

Discussion

Our patient's symptoms, which developed twice after introduction of MMF, are similar to the acute inflammatory syndrome previously described by Maes et al in 2 patients with Wegener's granulomatosis (6) and in a renal transplant recipient described by Hochegger et al (7).

Maes et al speculated that mycophenolic acid acyl glucuronide, a product of mycophenolic acid degradation, may induce proinflammatory cytokine expression in human mononuclear cells, as determined by Wieland et al (9). They initially postulated that a higher concentration of mycophenolic acid acyl glucuronide, an active metabolite with these potentially proinflammatory properties, might be a response unique to patients with Wegener's granulomatosis. This is unlikely to be a disease-specific effect because acute inflammatory syndrome has been subsequently described by Hochegger et al in a patient receiving MMF after renal transplantation due to glomerulosclerosis, and now in our patient with SLE (7).

Hochegger et al determined that in their patient with renal transplant, there was a paradoxical increase in reactive oxygen species production when polymorphonuclear cells from the patient were stimulated in vitro with 2 different stimuli in the presence of MMF. They hypothesized that the paradoxical reaction to MMF in their patient may have been due to simultaneous polymorphonuclear cell activation by an unknown proinflammatory stimulus (7).

Our patient has a history of primary biliary cirrhosis. Despite normal serum levels of liver enzymes and apparently normal synthetic function, it is possible that subtle liver disease altered the normal hepatic metabolism and detoxication of MMF. Liver disease was not a feature of the other reported cases of acute inflammatory syndrome.

The mechanism by which MMF may cause acute inflammatory syndrome is not completely understood. However, the possibility of this paradoxical inflammatory reaction to MMF must be considered in patients treated with MMF. Prompt discontinuation of the medication results in quick symptom resolution (as in our patient and the previously published cases). Moreover, the acute inflammatory syndrome may be mistaken for a flare of the disease being treated (SLE, Wegener's granulomatosis). If a brief trial of abstinence from MMF results in symptom resolution, unnecessary therapy for lupus or Wegener's granulomatosis may be avoided.

AUTHOR CONTRIBUTIONS

Dr. Konon had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study design. Konon.
Acquisition of data. Konon, Cronin.
Analysis and interpretation of data. Konon, Ryan.
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