Abstract

Anemia secondary to mycophenolate mofetil (MMF) was recently described in experimental animals. A clinical association between MMF and anemia has been observed, but there are no proven reports. We describe a girl with chronic graft failure who developed erythroid aplasia under immunosuppression with MMF. She showed prompt resolution when MMF was discontinued and a recurrence of this clinical course when MMF was restarted. As re-challenge with a medication is the most definitive approach for showing a direct relationship between the drug and the side effect, this case clearly demonstrates that MMF can cause erythroid aplasia.

Key words
Erythroid aplasia · Mycophenolate mofetil · Re-challenge · Renal transplantation

Introduction

Randomized clinical studies have shown that mycophenolate mofetil (MMF) is superior to azathioprine for preventing acute rejection in kidney transplant recipients [1]. There are also favorable data on MMF for kidney transplantation in children [2]. MMF inhibits the type II isomerase of inosine monophosphate dehydrogenase, a key enzyme of the de novo pathway of purine synthesis. Lymphocytes are selectively affected by MMF because of their dependence on the de novo pathway for proliferation, while other cells synthesize purines through the salvage pathway [3]. Erythropoiesis should not be affected by MMF, since red blood cell precursors utilize the salvage pathway [4]. Anemia secondary to MMF was recently described in experimental animals [5]. Clinical studies showed the occurrence of anemia under MMF therapy but there are no reports of a causal relationship in patients [1, 8]. We describe a patient who had reversible and reproducible erythroid aplasia due to MMF.

Case report

A 16-year-old girl with nephropathic cystinosis received a renal transplant from her mother at the age of 12 years. Her initial immunosuppressive regimen was cyclosporine A and prednisone. At 15 years, because of chronic graft dysfunction, her immunosuppression was changed to prednisone, tacrolimus, and MMF (1.2 g/day). At a glomerular filtration rate (GFR) of 25 ml/min per 1.73 m², subcutaneous recombinant human erythropoietin (EPO) at 250 IU/kg per week and iron supplementation were instituted, and her hemoglobin remained stable at 10 g/dl.

Eight months after initiation of MMF and tacrolimus the patient had a routine clinic visit; she had no complaints at that time, except for an upper respiratory infection 2 weeks previously. She was found to have a hemoglobin of 5.2 g/dl and received a red blood cell transfusion. Along with MMF and tacrolimus, she was also receiving prednisone 5 mg/day, thyroxine, furosemide, calcitriol, dihydralazine, and cysteamine.

Two weeks later she complained of fatigue and weight loss, and was admitted to the hospital with a hemoglobin of 4.2 g/dl. Her laboratory results included a white blood cell count of 4.6/nl, a platelet count of 540/nl, a lactic dehydrogenase of 350 U/l (normal=234–282), an iron saturation of 75%, a creatinine of 4 mg/dl (GFR 19 ml/min per 1.73 m², calculated by the Schwartz formula), total serum protein 6.4 g/dl, albumin 3.7 g/dl, and a reticulocyte count that was significantly suppressed at 6 promille (corrected reticulocyte count was 2.0 promille). Her tacrolimus trough level was 5.4 ng/ml. She received two units of packed red blood cells and her subcutaneous EPO dose was increased to 800 IU/kg per week. Her post-transfusion hemoglobin was 8 g/dl, but within 1 week her hemoglobin dropped to 5.1 g/dl. She had no overt signs of blood loss and her stool was negative for blood. Bone marrow aspiration confirmed erythroid aplasia. She had no signs of a recent parvovirus B19 infection based on negative serology and a negative bone marrow polymerase chain reaction-based assay (PCR) for virus; serology for cytomegalovirus and Epstein-Barr virus was also negative. MMF was discontinued, tacrolimus was given at the same dose, and, after another blood transfusion, the patient was discharged with a hemoglobin of 7.5 g/dl. Subcutaneous EPO was continued at 330 IU/kg per week. Two weeks later her hemoglobin was 8.3 g/dl.

The patient’s hemoglobin 4 months later was 12.9 g/dl and her EPO dose had been titrated down to 110 IU/kg per week. At this point MMF was restarted at a lower dose (1 g/day). Six weeks la-
After the patient had symptoms of fatigue, pallor, and loss of appetite; her hemoglobin was 6.8 g/dl. The MMF was again discontinued and the patient’s hemoglobin returned to 12 g/dl within 4 weeks. The patient’s hemoglobin has subsequently remained stable, and there has been no significant deterioration of transplant function (Fig. 1).

**Fig. 1** Changes in hemoglobin (Hb) level in a 16-year-old girl with chronic renal graft failure. Grey bars indicate initial mycophenolate mofetil (MMF) exposure and re-challenge. MMF caused reproducible erythroid aplasia.

## Discussion

Initially, our patient’s anemia seemed unlikely to be secondary to MMF. However, we rapidly excluded common causes, such as non-compliance, iron deficiency, dysfunctional bleeding, or underdosage of EPO [6]. The patient’s low reticulocyte count suggested that she had a problem with red blood cell production. We therefore performed a bone marrow biopsy to exclude a malignancy, a known complication in kidney transplant recipients. Because the bone marrow biopsy showed erythroid aplasia, we considered other explanations. Parvovirus B19 infection, a well-described cause of red cell aplasia, was excluded by serological tests and PCR-based assay of the bone marrow.

Because we found no clear explanation for our patient’s transfusion-dependent and potentially life-threatening erythroid aplasia – and as MMF was the only apparent antiproliferative drug in our patient – we withdrew MMF from the immunosuppressive regimen. As shown in Fig. 1, the patient’s hemoglobin normalized, leading to a temporary cessation of EPO. Tacrolimus has been described to induce pure red cell anemia [7], but none of these cases prove direct causation, since MMF was never restarted. Our patient had a recurrence of her anemia when MMF was restarted and prompt resolution when MMF was discontinued permanently. Re-challenge with a medication is the most-definitive approach for showing a direct relationship between the drug and the side effect.

However, our data are not sufficient to delineate the pathogenetic mechanisms. Pharmacokinetic studies showed enhanced myelosuppressive effects associated with increased mycophenolic acid levels when MMF is given together with tacrolimus [9]. In patients with renal failure, high levels of the glucuronide derivative of mycophenolic acid decrease protein binding of mycophenolic acid and therefore increase the myelosuppressive effect and risk for MMF-related toxicity [10]. Nonspecific myelosuppression should also lead to leukopenia or lymphopenia, but these were absent in our patient. It is also possible that she might have a lower threshold for suppression of erythropoiesis than the general population. There are no data suggesting an association between cystinosis and atypical purine synthesis. However, stimulated stem cells [11] or cell pools with high turnover, such as erythroleukemic cells [12], may switch pathways of purine synthesis from the salvage pathway to the de novo synthesis, increasing their sensitivity to MMF about five times. A similar metabolic situation might be found during intermittent therapy with high doses of subcutaneous recombinant EPO, as in our patient. MMF could therefore be a risk factor for EPO unresponsiveness in transplant recipients with chronic renal failure. Future studies are necessary to delineate the pharmacogenetic risk factors that are associated with these apparently idiosyncratic adverse events. At present we can only conclude that MMF should be considered in the differential diagnosis of erythroid aplasia.

## References


