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Microangiopathic Hemolytic Anemia Complicating FK506 (Tacrolimus) Therapy

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We describe 3 episodes of microangiopathic hemolytic anemia (MAHA) in 2 solid organ recipients under FK506 (tacrolimus) therapy. In both cases, discontinuation of FK506 and treatment with plasma exchange, fresh frozen plasma replacement, corticosteroids, aspirin, and dipyridamole led to resolution of MAHA. In one patient, reintroduction of FK506 led to rapid recurrence of MAHA. FK506-associated MAHA is probably rare but physicians must be aware of this severe complication. In our experience and according to the literature, FK506 does not seem to cross-react with cyclosporin A (CyA), an immunosuppressive drug already known to induce MAHA. © 1996 Wiley-Liss, Inc.

Key words: microangiopathic hemolytic anemia, hemolysis, FK506, tacrolimus

INTRODUCTION

FK506 (tacrolimus) is a recently introduced macrolide with potent immunosuppressive activity and represents an important advance in the management of organ recipients. Although FK506 and the cyclic polypeptide cyclosporin A (CyA) are totally different in structure and bind to different cytosolic proteins (FK506-binding protein and cyclophilin) [1], both exert similar selective antilymphocyte activity in vitro. They both inhibit interleukin-2 (IL-2) synthesis and other cytokines (IL-3, IL-4, tumor necrosis factor, and interferon gamma) at the mRNA transcription level leading to selective suppression of T-cell function [2]. FK506 and CyA share some pharmacological properties and some side effects: nephrotoxicity, neurotoxicity, HTA, diabetogenesis [3]. Microangiopathic hemolytic anemia (MAHA) is a well-documented complication of CyA following organ and bone marrow transplantation [4] but has seldom been associated with FK506. Here we report three episodes of MAHA in two solid organ recipients. Detailed analysis of hematological and biological parameters suggests that FK506 was the most likely cause of MAHA.

CASE REPORTS

Patient 1

A 53-year-old Caribbean male received a heart transplant in September 1993 for end stage heart failure due to alcoholic cardiomyopathy. Initial post transplant immunosuppression consisted of CyA, prednisone, and azathioprine, but because of 3 episodes of rejection, CyA was replaced by FK506 in June 1994. In March 1995, blood count showed pancytopenia with agranulocytosis: Hb 9 g/dL, white blood cells (WBC) count 0.7×10^9/L, neutrophils 0.39×10^9/L, platelets 72×10^9/L. At that time, medication was FK506 12 mg/day, prednisone 50 mg/day, and azathioprine 50 mg/day. Azathioprine was discontinued and he was hospitalized.

On admission, he presented with severe oral candidiasis and a pulmonary infiltrate. Bronchial washings revealed Aspergillus fumigatus and cytomegalovirus (CMV). In addition he had herpetic oesophagitis. Pancytopenia was attributed to azathioprine and to infection. He was treated with amphotericin B, acyclovir, and gancyclovir.

In April, anemia progressed and he became markedly thrombocytopenic, with Hb 7.1 g/dL, reticulocytes 186×10^9/L, WBC count 8.4×10^9/L, and platelets 36×10^9/L. A blood smear revealed the presence of numerous schizocytes. LDH was 2,034 U/L, total bilirubin 22 μmol/L, creatinine 242 μmol/L, and serum haptoglobin was less than 65 mg/L. Coagulation profile was normal and serum antiglobulin test negative. FK506 serum

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level was 22 μg/L. MAHA was diagnosed and FK506 was suspected as the causative agent. FK506 was discontinued and therapy begun with plasma exchange, fresh frozen plasma replacement, prednisone, dipyridamole, aspirin, and prostacyclin. Platelet count reached a nadir of 10×10^9/L.

After 3 weeks of treatment, gradual hematological improvement was noted (Hb 8g/dL, reticulocytes 89×10^9/L, LDH 683 U/L, creatinine 125 μmol/L), however, thrombocytopenia persisted (platelets 25×10^9/L) with megakaryocytic hypoplasia attributed to CMV infection. Although FK506 was suspected to have caused MAHA, it was decided to reintroduce it since the patient had been treated with FK506 for 10 months without developing hemolysis and MAHA had occurred in a severe infectious context.

FK506 was cautiously reintroduced. When FK506 serum level reached 5 μg/L, Hb fell to 6.8 g/dL, reticulocytes rose to 207×10^9/L, platelets were 33×10^9/L, LDH 1902 U/L, haptoglobin was undetectable, and blood smear showed numerous schizocytes. Recurrence of MAHA was diagnosed and FK506 discontinued. When platelets fell to 12×10^9/L, treatment of MAHA was resumed leading to resolution of hemolysis after 10 days. Moderate thrombocytopenia persisted after recovery. Immunosuppression was continued with prednisone and azathioprine only. One month later, CMV viremia developed, followed by multiorgan failure, and the patient died of massive upper GI bleeding without any evidence of cardiac rejection.

Patient 2

A 62-year-old Italian male underwent liver transplantation in March 1995 for end stage hepatic cirrhosis due to viral hepatitis C. Post transplant immunosuppression consisted of prednisone, CyA, and azathioprine. In May 1995, he was treated with OKT3 for rejection and CyA was replaced by FK506. In July, he started to develop acute renal failure (urea 16 mmol/L, creatinine 121 μmol/L) with FK506 serum level reaching 52.5 μg/L. One week later, blood count revealed anemia (Hb 7.1 g/dL), thrombocytopenia (40×10^9/L), and reticulocytosis (145×10^9/L). Coagulation profile was normal, direct human antiglobulin test negative, and haptoglobin <60 mg/L. Blood smear showed numerous schizocytes. MAHA was diagnosed and FK506 discontinued. Treatment consisted of 4 courses of plasma exchange with fresh frozen plasma replacement, methylprednisolone, aspirin, and dipyridamole leading to a rapid resolution of MAHA.

After recovery, CyA was cautiously reintroduced without recurrence of MAHA. One month later, the patient presented Klebsiella pneumoniae septicemia, pulmonary aspergillosis and multiple organ failure developed. He died without evidence of liver rejection.

DISCUSSION

MAHA may have different etiologies in connection with organ transplantation: organ rejection, CyA, infection [5]. In our cases, MAHA occurred without concomitant organ rejection, without CyA administration, and although in patient 1 it developed in an infectious context, rapid recovery despite persistent severe infection strongly argues against infection-associated MAHA. Although we cannot formally exclude idiopathic hemolytic-uremic syndrome (HUS) following viral infection, we believe that FK506 is the most likely cause of MAHA in our two patients. Patient 1 had a first eipsode of MAHA concomitant with high FK506 serum level and MAHA relapsed 8 days after reintroduction of FK506 (Fig. 1). Patient 2 had onset of MAHA following very high FK506 serum level due to renal failure. All three episodes resolved rapidly after FK506 discontinuation. It is noteworthy that the first episode of MAHA in Patient 1 followed high FK506 serum level whereas the second episode occurred despite normal FK506 serum value. This suggests that FK506 associated MAHA may not be correlated with high FK506 serum level.

CyA is well established as an etiological factor in MAHA [4]. Since the mechanisms of immunosuppression of FK506 and CyA are remarkably similar, it is not surprising that both drugs share some side effects, like MAHA.

To our knowledge, so far, FK506 has been implicated twice as the cause of MAHA. The first case was a renal transplant recipient who developed MAHA under FK506 therapy with favourable outcome once FK506 was discontinued and treatment with plasma exchange and fresh frozen plasma replacement instituted [6]. The second case of MAHA was reported in a bone marrow transplant recipient with refractory chronic graft-vs.-host disease treated with FK506; despite aggressive therapy (plasma infusion, methylprednisolone, and heparin) the patient died of multiorgan failure [7].

Although MAHA may be a complication of CyA and FK506 therapy, the use of drugs in cases of idiopathic HUS is not contraindicated nor is there necessarily a cross reaction between the two drugs. In fact, McCauley et al. [8] reported the successful treatment of CyA-induced HUS with FK506 and Scantlebury et al. [9] described a series of 11 cases of kidney transplantation for renal failure due to HUS treated with either CyA or FK506 as the main immunosuppressive agent. No microangiopathic complication was observed in any of these cases.

FK506 is very effective in the treatment of graft rejection. Although MAHA during FK506 therapy is probably rare, physicians should be aware of this severe complication. Blood count should be monitored regularly in patients receiving FK506, and if hemoglobin or platelets

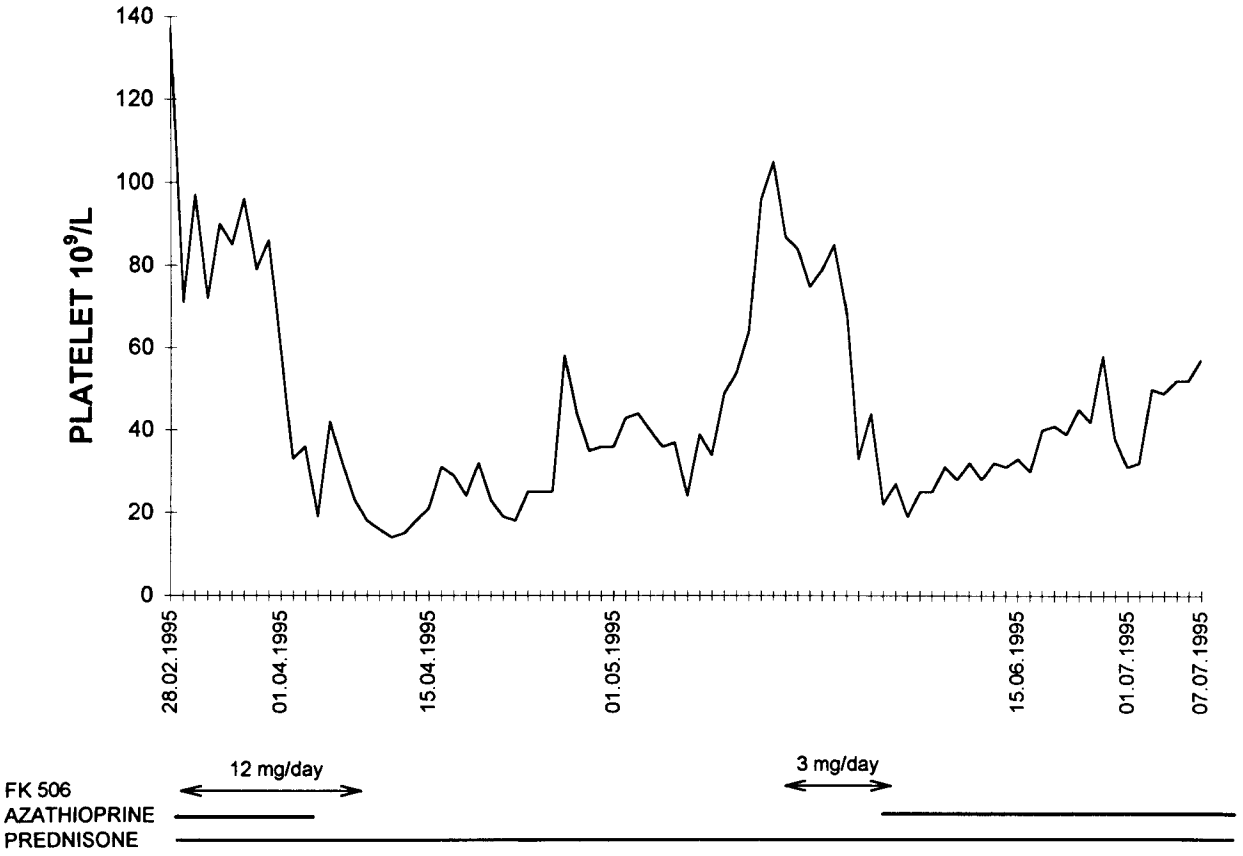

Fig. 1. Evolution of platelet count in relation to FK506 treatment in patient 1. It is clearly seen that reintroduction of FK506 was followed by MAHA relapse.

fall, a blood smear looking for schizocytes should be performed.

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