Case Report

Mycophenolate Mofetil Induced Myopathy in a Patient with Lupus Nephritis

MARÍA GALINDO, ANA CABELLO, BEATRIZ JOVEN, ANA ALONSO, PATRICIA CARREIRA, JESÚS PORTA, JOSÉ RAMÓN RICOY, ISABEL MATEO, and JOSÉ L. PABLOS

ABSTRACT. We describe a case of mycophenolate mofetil (MMF) induced myopathy in a patient with lupus nephritis. Two months after starting MMF treatment she developed asthenia, lower limb weakness, and abnormal increase of muscle enzymes. An electromyogram showed a myogenic pattern with small polyphasic discharges without neurogenic signs involving proximal muscles of lower limbs. Muscle biopsy revealed the presence of fibers of variable size with irregular sarcoplasmic basophilic areas. Using oxidative enzyme techniques, many type I fibers showed a moth-eaten appearance resembling minicores. The ultrastructural findings consisted of myofibrillary lesions with multiple small foci of Z-band streaming. MMF withdrawal was followed by complete clinical and enzymatic recovery. (J Rheumatol 2005;32:188–90)

Key Indexing Terms:
MYCOPHENOLATE MOFETIL TOXICITY MYOPATHY SYSTEMIC LUPUS ERYTHEMATOSUS

Renal disease is one of the most serious manifestations of systemic lupus erythematosus (SLE). Clinical evidence of renal involvement is found in one-half to two-thirds of patients with SLE[1]. Therapeutic management depends on the activity and severity of the renal lesion. At present, cyclophosphamide (CYC) plus corticosteroid is the standard initial treatment of severe proliferative glomerulonephritis, and its efficacy has been demonstrated in randomized controlled trials[2,3]. However, this therapy often results in immediate or cumulative adverse events such as increased risk of infection, bone marrow suppression, gonadal toxicity, hemorrhagic cystitis, or malignancy. Further, the optimal dose, route, and duration of CYC administration remain controversial, and about one-fourth of patients with proliferative glomerulonephritis are refractory to this treatment[3].

Data from uncontrolled series and, more recently, from prospective and controlled trials suggest that mycophenolate mofetil (MMF) is an effective and safe option in the treatment of lupus nephritis[4-6]. The most common side effects of MMF are gastrointestinal symptoms including diarrhea, vomiting, and abdominal pain, and leukopenia. Usually, these effects disappear with dose reduction. We describe a toxic myopathy with remarkable pathological features as a previously unreported complication in a patient treated with MMF due to SLE renal disease.

From the Rheumatology, Pathology, and Neurology Units, Hospital 12 de Octubre, Madrid, Spain.

M. Galindo, MD, Rheumatology Unit; A. Cabello, MD, Pathology Unit; B. Joven, MD, Rheumatology Unit; A. Alonso, MD, Neurology Unit; P. Carreira, MD, Rheumatology Unit; J. Porta, MD, Neurology Unit; J.R. Ricoy, MD, Pathology Unit; I. Mateo, MD; J.L. Pablos, MD, Rheumatology Unit.

Address reprint requests to Dr. M. Galindo, Servicio de Reumatología, Hospital 12 de Octubre, Carretera de Andalucía Km 5.4, 28041 Madrid, Spain. E-mail: reuma@h12o.es

Submitted April 7, 2004; revision accepted July 30, 2004.

CASE REPORT

A 31-year-old black woman was admitted because of lower limb pain and weakness. She had been diagnosed with SLE in 1999, when she developed malar rash, mouth ulcers, inflammatory arthralgias, severe thrombopenia, and leukolymphopenia, with positive antinuclear, anti-double-stranded DNA, anti-Ro, and anticardiolipin antibodies. Therapy with high doses of steroids, intravenous gammaglobulin, and azathioprine was started. Two months later, she suffered an early pregnancy loss that was followed by the development of nephritis with proteinuria (< 1 g/day), hematuria, and leukocyturia. Renal biopsy revealed a WHO class III lupus nephritis, and monthly intravenous CYC pulses were started. During CYC treatment, she developed *Salmonella enteritidis* bacteremia and became a chronic carrier. In spite of leukopenia, infection, and poor adherence to CYC therapy, after 31 months she had received an accumulated dose of 14,400 mg CYC. At that time, SLE and nephritis remained active, with proteinuria > 2 g/day, severe leukolymphopenia, and anemia with positive Coombs test, positive anti-double-stranded DNA, and low C3 and C4 levels. CYC was withdrawn and MMF was started and maintained at 1.5 g/day because of diarrhea with higher doses. Two months later, she was admitted because of asthenia, lower limb weakness, and abnormal increase of muscle enzymes. On admission she was taking prednisolone 30 mg/day, MMF 1.5 g/day, aspirin 100 mg/day, omeprazole 20 mg/day, enalapril 10 mg/day, folic acid 5 mg/day, and oral iron supplement. Examination was unremarkable and muscle strength tests were normal. Family history for myopathy was negative.

Laboratory findings revealed the presence of microcytic anemia, leukopenia (1900 leukocytes/mm^3) with lymphopenia, elevated erythrocyte sedimentation rate and gammaglobulin levels, and elevated muscle enzymes [creatine kinase (CK) 429 IU/l (normal 20–130); lactate dehydrogenase 619 IU/l (90–230); GOT 63 IU/l (5–45); GPT 120 IU/l (5–45)]. Thyroid function was normal, and electrocardiogram, thorax radiograph, and abdominal echography revealed no abnormal findings. A slight mitral valve insufficiency with no valve prolapse and a minimal pericardial effusion were present on echocardiography. During hospitalization, she devel-

oped dysuria, and *S. enteritidis* was isolated in blood and urine cultures. Infection resolved after one week of intravenous ceftriaxone.

An electromyogram showed a myogenic pattern with small polyphasic discharges involving proximal muscles of lower limbs. No neurogenic signs were present. A muscle biopsy showed the presence of fibers of variable size with irregular sarcoplasmic basophilic areas with hematoxylin-eosin staining (Figure 1A, 1B). With oxidative enzyme techniques, many type I fibers showed a moth-eaten appearance, with multiple irregular overstained areas together with focal losses of enzyme activity (Figure 1C, 1D). These areas were similar to minicores. The ultrastructural findings confirmed the myofibrillary lesions, with multiple small foci of Z-band streaming. Inflammatory cell infiltration, necrotic fibers, and type 2 fiber atrophy were not observed, excluding SLE associated inflammatory myopathy or glucocorticoid induced myopathy. MMF withdrawal was followed by a rapid decrease of CK, reaching normal levels 2 weeks after withdrawal. A progressive clinical improvement with a complete normalization of weakness was observed 3 months later.

DISCUSSION

MMF is hydrolyzed to mycophenolic acid, the active immunosuppressant compound that is a reversible noncompetitive inhibitor of the enzyme inosine monophosphate dehydrogenase, a rate-limiting enzyme in the *de novo* synthesis of purines. MMF has been widely used in solid organ transplant, and recently several reports have suggested its potential efficacy in immune mediated diseases such as autoimmune neuromuscular disorders or glomerulonephritis in patients with SLE[4-7]. The toxicity profile of MMF appears better than that of CYC, and it has been restricted to gastrointestinal symptoms or leukopenia, usually reversed by dose reduction. However, in large series of patients with solid organ transplant or psoriasis, other rare adverse events have been reported, including opportunistic infections, malignancy, or scalp hair loss[8-10]. To our knowledge, this is the first report describing muscular toxicity of MMF. Geilen, *et al*, described the development of muscle pain requiring withdrawal of MMF in one out of a group of 11 patients with severe psoriasis treated with MMF. This patient referred muscle pain coincidental to MMF administration but he did not present muscle enzyme elevation[11].

Our patient developed a proximal myopathy with enzyme elevation, a myopathic electromyogram, and an uncommon pathological picture. The presence of minicores in muscle fibers is characteristic of a congenital myopathy, multiminicore disease, whose genetic abnormalities are under investigation. In some families, the disease is associated with mutations in the ryanodine receptor gene[12], whereas in others, the selenoprotein-N gene is mutated[13]. In a nonspecific way, minicores may be found in several unrelated diseases such as hypothyroid myopathy, denervation atrophy, and metabolic myopathies[14]. This myopathic pattern is exceptionally observed in drug induced myopathies, and to our knowledge it has only been reported associated to emetine induced muscular toxicity[15]. Genetic and clinical heterogeneity of myopathies with minicores makes it difficult to define their incidence. In the last 30 years, the estimated cumulative incidence in our hospital was 20 findings

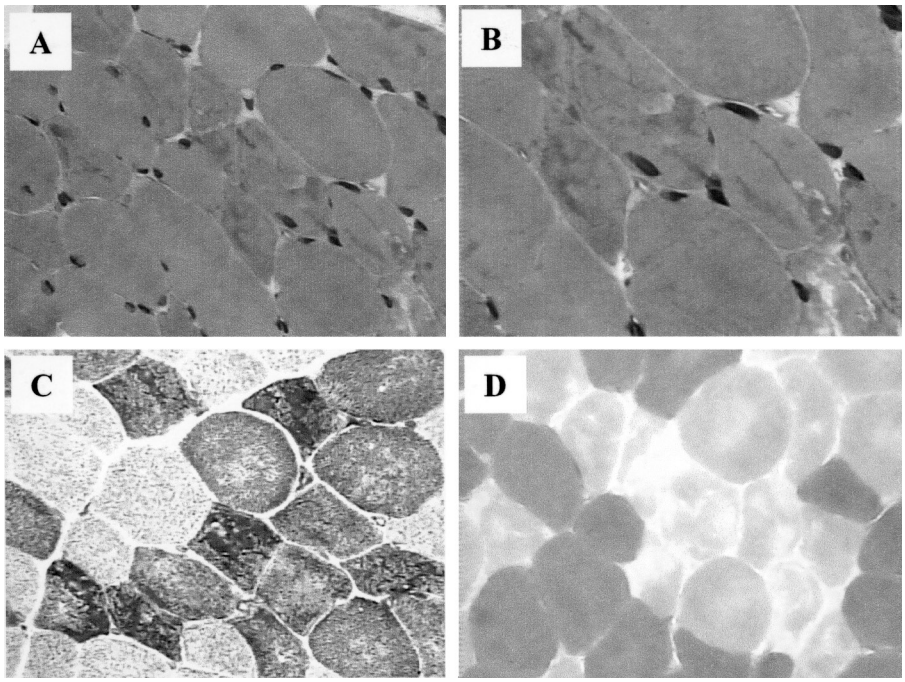

Figure 1. Histopathological features of muscle biopsy. Irregular basophilic and vacuolar lesions in the sarcoplasm of abundant muscle fibers by H&E staining (A, B). The lesions were identified as focal losses of enzyme activity in DPNH positive (C) and ATPase pH 9.4 negative (D) type I fibers (magnification A, C, D: ×400; B: ×630).

of congenital minicore myopathy in 8700 muscular biopsies. No data regarding the role of individual susceptibility have been reported.

Our observation suggests that, although overt myopathy seems a rare event during MMF use, increased awareness of the potential muscular toxicity of MMF is recommended.

REFERENCES

1. Cameron JS. Lupus nephritis. J Am Soc Nephrol 1999;10:413-24.
2. Austin HA III, Klippel JH, Balow JE, et al. Therapy of lupus nephritis: controlled trial of prednisone and cytotoxic drugs. N Engl J Med 1986;314:614-9.
3. Takada K, Illei GG, Boumpas DT. Cyclophosphamide for the treatment of systemic lupus erythematosus. Lupus 2001;10:154-61.
4. Dooley MA, Cosio FG, Nachman PH, et al. Mycophenolate mofetil therapy in lupus nephritis: clinical observations. J Am Soc Nephrol 1999;10:833-9.
5. Chan TM, Li FK, Tang CS, et al. Efficacy of mycophenolate mofetil in patients with diffuse proliferative lupus nephritis. Hong Kong-Guangzhou Nephrology Study Group. N Engl J Med 2000;343:1156-62.
6. Kingdon EJ, McLean AG, Psimenou E, et al. The safety and efficacy of MMF in lupus nephritis: a pilot study. Lupus 2001;10:606-11.
7. Jayne DRW. Non transplant uses of mycophenolate mofetil. Curr Opin Nephrol Hypertens 1999;8:563-7.
8. Epinette WW, Parker CM, Jones EL, Greist MC. Mycophenolic acid for psoriasis: a review of pharmacology, long-term efficacy, and safety. J Am Acad Dermatol 1987;17:962-71.
9. The Tricontinental Mycophenolate Mofetil Renal Transplantation Study Group. A blinded, randomized clinical trial of mycophenolate mofetil for the prevention of acute rejection in cadaveric renal transplantation. Transplantation 1996;61:1029-37.
10. Pfitzmann R, Klupp J, Langrehr JM, et al. Mycophenolate mofetil for immunosuppression after liver transplantation: a follow-up study of 191 patients. Transplantation 2003;76:130-6.
11. Geilen CC, Arnold M, Orfanos CE. Mycophenolate mofetil as a systemic antipsoriatic agent: positive experience in 11 patients. Br J Dermatol 2001;144:583-6.
12. Ferreiro A, Monnier N, Romero NB, et al. A recessive form of central core disease, transiently presenting as multi-minicore disease, is associated with a homozygous mutation in the ryanodine receptor type 1 gene. Ann Neurol 2002;51:750-9.
13. Ferreiro A, Quijano-Roy S, Pichereau C, et al. Mutations of the selenoprotein N gene, which is implicated in rigid spine muscular dystrophy, cause the classical phenotype of multiminicore disease: reassessing the nosology of early-onset myopathies. Am J Hum Genet 2002;71:739-49.
14. Ferreiro A, Estournet B, Chateau D, et al. Multi-minicore disease — searching for boundaries: phenotype analysis of 38 cases. Ann Neurol 2000;48:745-57.
15. Duane DD, Engel AG. Emetine myopathy. Neurology 1970;20:733-9.