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Short communication

Polymyositis in solid organ transplant recipients receiving tacrolimus

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ABSTRACT

Tacrolimus, also known as FK506, is an immunosuppressive agent widely used for the prevention of acute allograft rejection in organ transplantation and for the treatment of immunological diseases. This study reports two male patients who underwent solid organ transplantation (liver and kidney). After transplant, the patients received continuous immunosuppressive therapy with oral tacrolimus and later presented clinical manifestations and laboratory signs of myopathy. Muscle biopsies of both patients clearly documented an inflammatory myopathy with the histological features of polymyositis including CD8 + T cells which invaded healthy muscle fibers and expressed granzyme B and perforin, many CD68 + macrophages and MHC class I antigen upregulation on the surface of most fibers. Because of the temporal association while receiving tacrolimus and since other possible causes for myopathy were excluded, the most likely cause of polymyositis in our patients was tacrolimus toxicity. We suggest that patients on tacrolimus should be carefully monitored for serum CK levels and clinical signs of muscle disease.

1. Introduction

Tacrolimus (FK506) is a calcineurin inhibitor widely used as potent immunosuppressant agent for the prevention of rejection in solid organ transplantation [1,2]. The drug was also introduced in the therapy of several autoimmune diseases including myasthenia gravis and difficult-to-treat cases of polymyositis [3]. In addition, calcineurin inhibitors have been proposed among second-line agents for treatment of myositis and polymyositis, the only "distinctive" neurological manifestations in chronic graft-versus-host diseases (GVHD), a syndrome characterized by immune-mediated multisystemic inflammation occurring after allogeneic hematopoietic stem cell transplantation (HSCT) [4,5].

One study reported a renal transplant patient who had, 10 months after he was started on tacrolimus, an inflammatory myopathy which resolved by its withdrawal [6]. We describe a patient who developed myositis after immunosuppressive treatment with FK506, and performed a detailed analysis of the pathological features of muscle biopsy from this patient and the previous one.

2. Case reports

2.1. Patient 1

This 62-year-old male patient underwent living-donor liver transplantation for alcohol-related cirrhosis two years before. After liver transplant, the patient received continuous immunosuppressive therapy with 1 mg of oral tacrolimus per day. His past medical history disclosed hypertension and diabetes and therapy included low dose of insulin, furosemide, allopurinol and ursodeoxycholic acid. Twenty-one months after the transplantation, the patient developed bile duct stenosis and investigation showed increased levels of serum creatine kinase (CK) (1880 U/L; normal < 200), lactate dehydrogenase (852 U/L; normal < 450), aspartate aminotransferase (160 U/L; normal < 50) and alanine aminotransferase (171 U/L; normal < 50). CK levels were persistently elevated (1600 U/L); electroneurography and needle electromyography documented an axonal peripheral neuropathy. At the time of our observation, three months later, on clinical examination the patient squatted and rose from the floor with difficulty and weakness of the thigh flexor (MRC 4) and quadriceps (MRC 4) muscles was present. Deep tendon reflexes were absent in the arms and legs and vibration sense was lost in the legs. At that time, an open muscle biopsy was obtained from the vastus lateralis. Two months later, the patient underwent surgery for bile duct stenosis but then he developed invasive aspergillosis and two weeks later he died.

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2.2. Patient 2

Clinical data have been previously reported [6]. Briefly a 53-year-old man with end-stage renal disease caused by chronic glomerulonephritis underwent a renal transplantation at age 40 and received a second renal graft six years later. A combination treatment of cyclosporine A and azathioprine was started after the second transplant. At age 52 the patient's immunosuppression was switched to tacrolimus, initially 5 mg per day, and within a month 4 mg daily because of high drug serum level. Ten months later the patient complained of muscle pain and laboratory investigations documented a mild increase of CK value, about two–three fold normal value. Because of persistent CK elevations over seven months, an open biopsy of the vastus lateralis muscle was performed. Tacrolimus was then withdrawn followed by resolution of the patient's symptoms and normalization of CK level. The patient was hepatitis C virus (HCV) positive with a viral load of 12.79 MEq/ml two months before muscle biopsy and he was treated with ribavirin which was stopped one month before the elevation of CK.

3. Materials and methods

3.1. Muscle biopsies

Muscle biopsies were obtained for diagnostic purposes with written informed consent and the study was approved by the local ethical board.

3.2. Histology and histochemistry

Serial 8-μm-thick cryosections were stained with standard histological and histochemical methods including hematoxylin and eosin, modified Gomori trichrome, ATPase (pH 4.3, 4.6 and 10.4), succinate dehydrogenase (SDH), cytochrome c oxidase (COX), nicotinamide adenine dinucleotide-tetrazolium reductase (NADH-TR), periodic acid Schiff, Sudan black stains and acid phosphatase.

3.3. Immunohistochemistry and confocal immunofluorescence microscopy

Immunohistochemical studies were performed on serial 6.5-μm-thick transverse muscle sections using the following well-characterized anti-human antibodies: anti-CD3, anti-CD8, anti-CD20, anti-CD25, anti-CD30, anti-CD57, anti-CD68, anti-MHC (major histocompatibility complex) class I, anti-Granzyme B and anti-Perforin. The reactions were revealed by peroxidase or immunofluorescence methods.

Double immunofluorescence was performed using antibodies to CD3 and CD68 in combination with an antibody to CD8. Confocal images were acquired with Zeiss LSM 510 confocal microscope.

To control staining specificity the primary antibody was omitted or replaced with nonimmune sera at the same concentration.

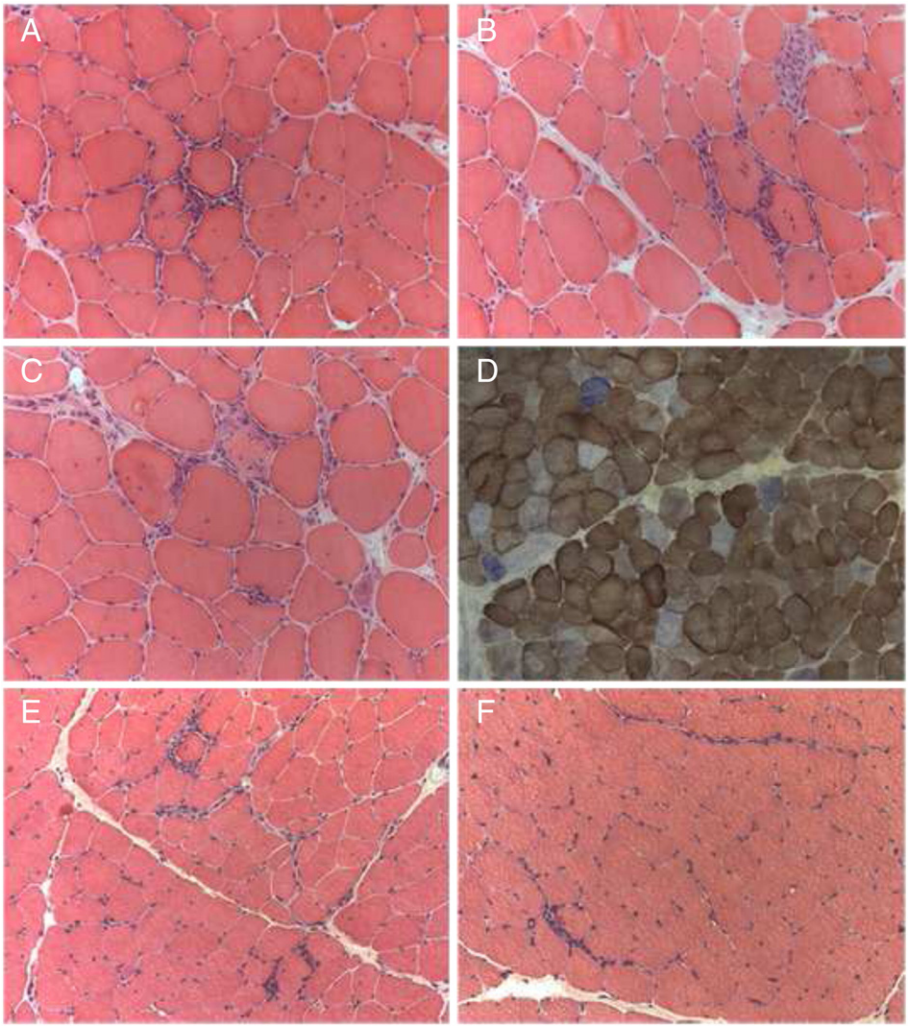

Fig. 1. Light microscopy of the muscle biopsies. Histological findings of patient 1 (A–D) and of patient 2 (E and F). A–C (hematoxylin and eosin): Two small endomysial inflammatory infiltrates surrounding and invading healthy muscle fibres (A and B); two necrotic muscle fibers, one of which is entirely invaded by inflammatory cells (B and C); a small basophilic regenerating fiber in C. D: Cytochrome c oxidase shows several COX negative muscle fibres. E, F (hematoxylin and eosin): Three endomysial inflammatory infiltrates surrounding non-necrotic muscle fibers.