

A case report of cyclosporine-induced myopathy with subacute muscular atrophy as initial presentation

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Abstract

Rationale: Cyclosporine A (CsA) is a potent immunosuppressive agent originally used to prevent rejection after organ transplantation but now more frequently used for treatment of refractory autoimmune diseases. It can induce adverse effects, such as nephrotoxicity, gastrointestinal reactions, and gingival hyperplasia whilst myopathy with subacute muscular atrophy are rare.

Patient concerns: A 55-year-old male patient with idiopathic membranous nephropathy treated with cyclosporine A at 3 mg/kg/d and prednisone at 0.5 mg/kg.d for more than 20 days, gradually developed lower limb weakness, which were progressively aggravated until he was unable to stand or walk. A physical examination show muscle atrophy of both lower extremities, which was more severe in the right thigh muscle than the left, decreased muscular tension of the limbs was also observed.

Diagnoses: Light microscopy and Transmission electron microscopy of muscle (quadriceps femoris) biopsy revealed drug-induced myopathy rather than neurogenic damage.

Interventions: Cyclosporine was withdrawn and replaced with cyclophosphamide tablets, prednisone remain unchanged and other symptomatic therapies were also administered.

Outcomes: His bilateral thigh muscle atrophy showed improvement and lower limb weakness was obviously alleviated and he could stand and walk with the help of others 4 weeks later. Gradually, his thigh muscle atrophy was alleviated so that he was able to walk independently. After follow-up, no similar symptoms were found in the patients.

Lessons: CsA-induced myopathy with muscular atrophy is rare and serious, which can be identified according to pathological characteristics.

Abbreviations: ATPase = adenosine triphosphatase, CaN = Calcineurin, COX = Cytochrome oxidase, CsA = cyclosporine A, FOXO = forehead transcription factor O, HE = hematoxylin-eosin, IGF-1 = Insulin-like growth factor 1, MCK = muscle creatine kinase, MGT = modified gomori trichrome, MRI = magnetic resonance imaging, NADH = reduced form of nicotinamide adenine dinucleotide, NFAT = nuclear factor of activated T cells, PGC-1 α = Peroxisome proliferator-activated receptor gamma coactivator 1-alpha, SHD = Succinate dehydrogenase, TEM = Transmission electron microscopy.

Keywords: cyclosporine A, idiopathic membranous nephropathy, myopathy, subacute muscular atrophy

1. Introduction

Cyclosporine A (CsA) is a potent immunosuppressive agent originally used to prevent rejection after organ transplantation but now more frequently used for treatment of refractory autoimmune diseases such as rheumatoid arthritis, systemic lupus

erythematosus, and refractory nephrotic syndrome.^[1] It can inhibit the cell-mediated immune reaction, B cell activity, production of T cell-dependent antibodies, and production and release of lymphoid factors such as interleukin 2 at the cellular level. It can induce adverse effects, such as nephrotoxicity, gastrointestinal reactions, and gingival hyperplasia whilst metabolic myopathy with subacute muscular atrophy are rare. Our study describes a rare case of CsA-induced myopathy initially presenting with subacute muscular atrophy. Informed written consent was obtained from the patient for publication of this case report and accompanying images.

2. Case report

A 55-year-old male patient without known chronic disease was admitted to our department with edema of the face and lower extremities, massive proteinuria and hypoproteinemia were found after admission. He was diagnosed with “nephrotic syndrome” and renal biopsy confirmed idiopathic membranous nephropathy. He was treated with cyclosporine A at 3 mg/kg/d and prednisone at 0.5 mg/kg.d. The patients was discharged from hospital after his serum CsA concentration met clinical standards, meanwhile, his CPK value was normal and symptomatic relief.

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More than 20 days later, gradually developed lower limb weakness, which were progressively aggravated until he was unable to stand or walk 1 month later. The patient was admitted again. A physical examination shows muscle atrophy of both lower extremities, which was more severe in the right thigh muscle than the left (Fig. 1), decreased muscular tension of the limbs was also observed (grade V muscular tension of upper limbs, grade II muscular tension of right lower limb and grade III muscular tension of left lower limb).



Figure 1. Signs of muscular atrophy in lower limbs of the case patient.

No abnormalities were found in myozyme spectrum, electrolytes, and thyroid function. Electromyography and nerve conduction tests showed myoelectric changes caused by myogenic damage. Thigh muscle MRI scan indicated:

1. muscle atrophy of the right thigh with edema of lateral femoral muscle, biceps femoris, and semimembranosus
2. swelling of bilateral external obturator and pectineus muscles, effusion in the intermuscular septum.

Histological examination of muscle (quadriceps femoris) biopsy samples revealed the muscle fibers were obviously different in size and atrophic fibers distributed in small clusters or foci among normal fibers (as shown by Fig. 2a). No broken red fibers and rimmed vacuoles were found (as shown by Fig. 2b). Reticular disorder was observed in local areas of muscle fibers stained with NADH (as shown by Fig. 2c). When muscle fibers stained with ATPase staining (as shown in Fig. 2d), Part IIB atrophy of muscle fibers were observed, but no signs of necrosis, phagocytic changes, or regenerative fibers were observed. No infiltration of inflammatory cells was seen in the intermuscular septum. In accord with histopathological analysis, TEM revealed atrophic changes in scattered muscle fibers, Myofascial collapse, and basement membrane folding were also observed (Fig. 3), which suggesting drug-induced myopathy rather than neurogenic damage.

Drug induced myopathy was highly suspicious, cyclosporine was withdrawn and replaced with cyclophosphamide tablets, prednisone remain unchanged and other symptomatic therapies were also administered. Four weeks later, bilateral thigh muscle atrophy showed improvement and lower limb weakness was obviously alleviated. Physical examination showed upper limb muscle strength of grade V, left lower limb muscle strength of grade IV, and right lower limb muscle strength of grade III. The patient could stand and walk with the help of others. He was discharged from the hospital and followed up regularly. Gradually, his thigh muscle atrophy was alleviated so that he was able to walk independently.

3. Discussion

Cyclosporine A-induced musculoskeletal diseases are rarely reported and CsA-induced muscle atrophy is even less common. To the best of our knowledge, this is the first report in medical literature of myopathy with subacute muscular atrophy associated with cyclosporine A. CsA-induced myopathy characterized by mitochondrial dysfunction is typically manifested as ragged red fibers, some COX-deficient fibers, disordered fibers stained with NADH and SDH, and intracellular lipid droplet aggregation.^[2] The pathological findings from COX, NADH, and SDH staining of biopsied muscle resembled common drug-induced myopathy characterized by mitochondrial dysfunction.

Cyclosporine A is an inhibitor of calcineurin (CaN, or protein phosphatase-3) the only serine/threonine phosphatase known to be regulated by calcium and calmodulin. Calcineurin has 3 subunits, CaN α , CaN β , and CaN γ , of which CaN α and CaN β are widely expressed in skeletal muscle.^[3,4] The activation of CaN may play an important role in the growth of skeletal muscle. Musaro et al found that IGF-1 mediates the growth of rhabdomy striated muscle cells by activating CaN and its downstream target NFAT transcription factor.^[5] Recently, CaN was found to have distinct effects on muscle growth and muscle mass maintenance among different muscle phenotypes, and to differentially affect

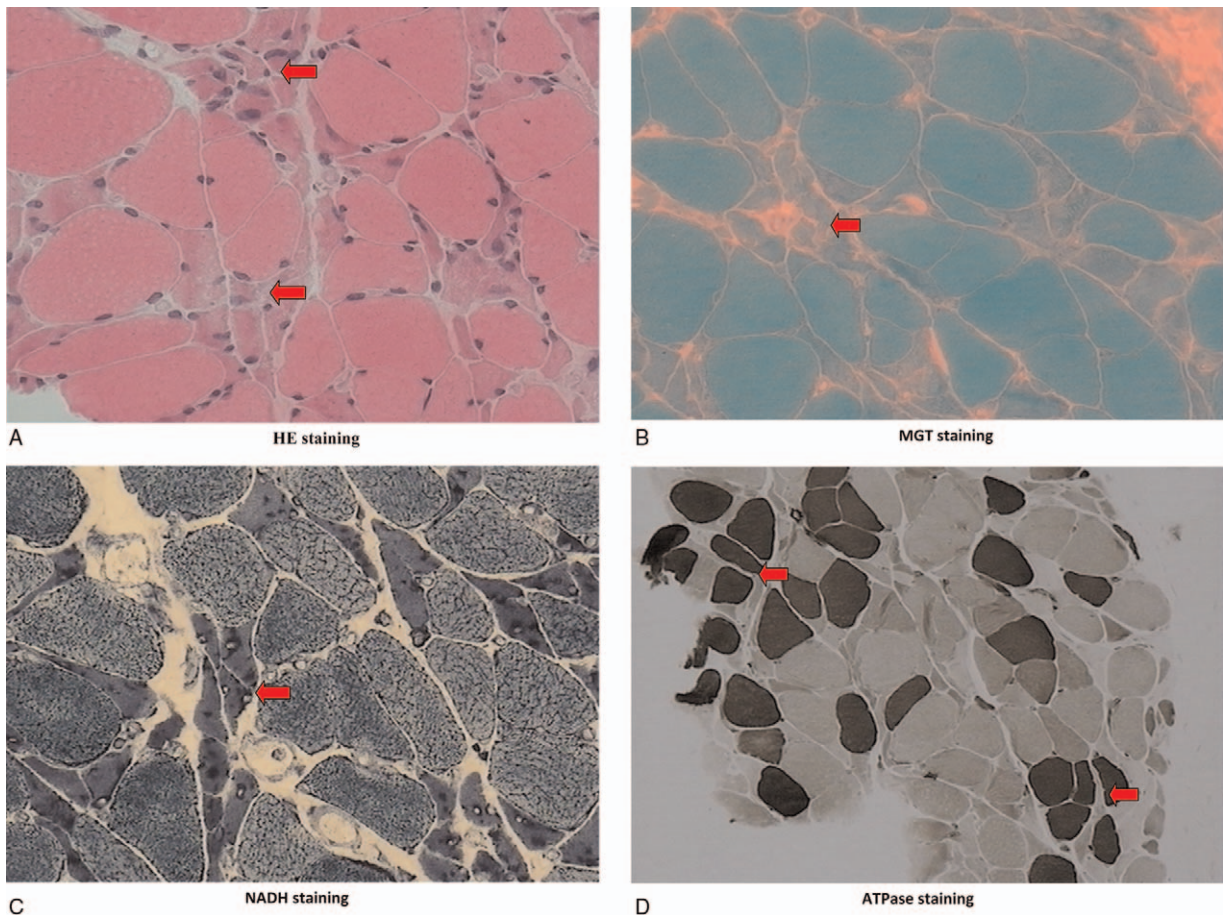


Figure 2. Light microscopy of muscle biopsy: a. HE staining: the muscle fibers were obviously different in size and atrophic fibers distributed in small clusters or foci among normal fibers; b. MGT staining: No broken red fibers and rimmed vacuoles were found; c. NADH staining: Reticular disorder was observed in local areas of muscle fibers; d. ATPase staining: Part IIB atrophy of muscle fibers were observed. NADH= reduced form of nicotinamide adenine dinucleotide, MGT = modified gomori trichrome.

muscle growth regulation and muscle mass maintenance according to muscle type and growth cycle.

Recent research has found that CaN can activate the expression of peroxisome proliferator-activated receptor- γ co-activator-1 α (PGC-1 α),^[6] a transcriptional co-activator that

promotes the transformation of type IIb muscle fibers into type I and type IIa muscle fibers by activating muscle creatine kinase (MCK).^[7] Further, PGC-1 α inhibits the ubiquitin-proteasome and autophagy-lysosome systems by suppressing forkhead transcription factor O (FOXO) expression, thereby preventing

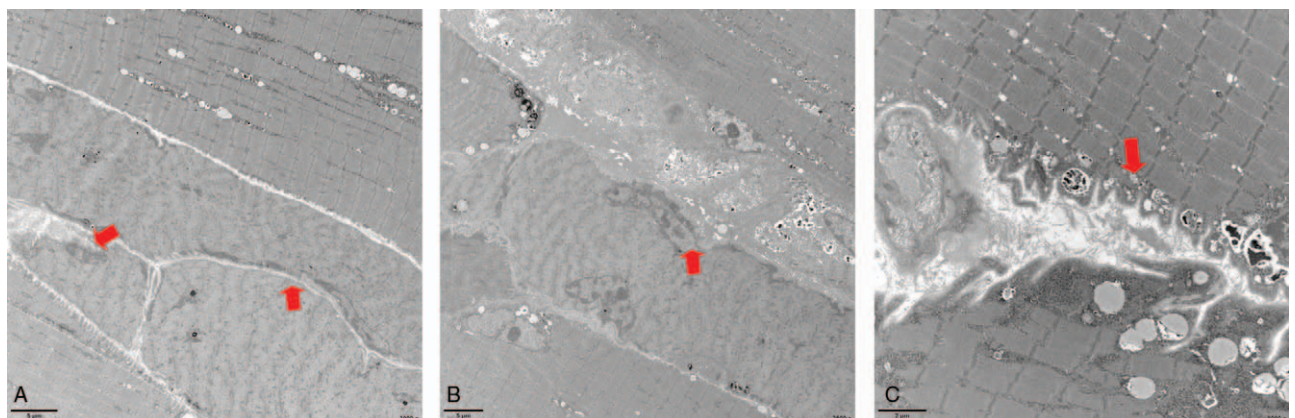


Figure 3. Transmission electron microscopy of quadriceps femoris biopsy atrophic changes in scattered muscle fibers, Myofascial collapse and basement membrane folding were also observed.

muscular atrophy.^[8] The expression of PGC-1 α mRNA was significantly lower in the hind leg muscles of CaN α -/- and CaN β -/- mice compared to wild-type mice, and overexpression of CaN in skeletal muscle led to the overexpression of PGC-1 α . These findings suggest that CaN signaling directly influences expression of PGC-1 α ^[9] and that CaN inhibitors (such as CsA) may suppress PGC-1 α expression and weaken the inhibitory effect on FOXO, leading to muscle atrophy. The IGF-1/PI3K/AKT signaling pathway is also strongly implicated in skeletal muscle hypertrophy and muscle protein synthesis.^[10] Some studies suggest that CaN inhibitors (such as CsA) can suppress the IGF-1/PI3K/AKT signaling pathway, dephosphorylate FOXO, and activate the ubiquitin-proteasome and autophagy-lysosome systems, thereby resulting in muscle atrophy.^[7]

In summary, CsA-induced myopathy with muscular atrophy is rare and serious, which can be identified according to pathological characteristics.

Author contributions

Data curation: Zhen Li, JianBin Zhang.

Investigation: Hongyun Ding, Zhen Li.

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References

- [1] Alrashedi MG, Ali AS, Ali SS, et al. Impact of thymoquinone on cyclosporine A pharmacokinetics and toxicity in rodents. *J Pharm Pharmacol* 2018;70:1332–9.
- [2] Franch HA, Price SR. Molecular signaling pathways regulating muscle proteolysis during atrophy. *Curr Opin Clin Nutr Metab Care* 2005; 8:271–5.
- [3] Klee CB, Ren H, Wang X. Regulation of the calmodulin-stimulated protein phosphatase, calcineurin. *J Biol Chem* 1998;273:13367–70.
- [4] Rusnak F, Mertz P. Calcineurin: form and function. *Physiol Rev* 2000;80:1483–521.
- [5] Musaro A, McCullagh KJ, Naya FJ, et al. IGF-1 induces skeletal myocyte hypertrophy through calcineurin in association with GATA-2 and NFATc1. *Nature* 1999;400:581–5.
- [6] Taylor EB, Lamb JD, Hurst RW, et al. Endurance training increases skeletal muscle LKB1 and PGC-1 α protein abundance: effects of time and intensity. *Am J Physiol Endocrinol metab* 2005;289: E960–8.
- [7] Marco S, Jiandie L, Christoph H, et al. PGC-1 protects skeletal muscle from atrophy by suppressing FoxO3 action and atrophy-specific gene transcription. *Proc Natl Acad Sci USA* 2006;103:16260–5.
- [8] Mammucari C, Milan G, Romanello V, et al. FoxO3 controls autophagy in skeletal muscle in vivo. *Cell Metabolism* 2007;6:458–71.
- [9] Guerfali I, Manissolle C, Durieux AC, et al. Calcineurin A and CaMKIV transactivate PGC-1 α promoter, but differentially regulate cytochrome c promoter in rat skeletal muscle. *Pflugers Arch* 2007;454:297–305.
- [10] Schiaffino S, Mammucari C. Regulation of skeletal muscle growth by the IGF1-Akt/PKB pathway: insights from genetic models. *Skelet Muscle* 2011;1:4.