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CASE REPORT

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Levofloxacin-induced Achilles tendon rupture in a patient with systemic microscopic polyangiitis

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Abstract We report a case of spontaneous Achilles tendon rupture associated with myeloperoxidase–anti-neutrophil cytoplasmic antibody (MPO-ANCA)-related microscopic polyangiitis in a 77-year-old man who was treated with oral corticosteroids. Several days after 10 days of treatment with levoflaxacin (daily dose 200 mg) for bacterial pneumonia, he noted discomfort around both Achilles tendons. The discomfort developed into swelling around his left ankle, and he could not walk well. We diagnosed bilateral Achilles tendinitis with spontaneous rupture induced by levofloxacin. Epidemiological studies show that the risk of fluoroquinolone-related tendon rupture is highest among patients over the age of 60 years who are receiving a corticosteroid. Rupture of the Achilles tendon is a rare but serious side effect of fluoroquinolone usage. Thus, physicians should be aware of this adverse effect, especially when prescribing medication for aged patients being treated with corticosteroids.

Key words Achilles tendinitis · Achilles tendon rupture · Fluoroquinolones · Microscopic polyangiitis · Steroid therapy

Introduction

Fluoroquinolones are antimicrobials commonly used because they have excellent gastrointestinal absorption, good tissue penetration, and broad-spectrum activity; moreover, they are thought to be relatively safe.[1] Although tendinitis and tendon rupture have been reported as rare side effects of fluoroquinolones,[2–4] recently emerging reports show an association between tendon rupture and the new fluoroquinolones, such as levofloxacin.[5–7] Here we present a case of nontraumatic rupture of the Achilles tendon induced by levofloxacin in a patient with systemic microscopic polyangiitis, an association that has not been previously described.

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Case report

The patient was a 77-year-old man who had begun to experience general malaise, high fever, and weight loss at the end of July 2003. He had a 5-year history of chronic obstructive pulmonary disease (COPD). He was found to have hematuria, proteinuria, and renal dysfunction (serum creatinine 4.5 mg/dl). As a high titer of myeloperoxidase-anti-neutrophil cytoplasmic antibody (MPO-ANCA) was identified, he was diagnosed as having rapidly progressive glomerulonephritis associated with microscopic polyangiitis. He was treated with pulse methylprednisolone therapy (0.5 g per day for 3 days) followed by oral prednisolone (PSL, 40 mg in tapering dose). His symptoms and renal function were improved, and he was discharged from our hospital. In November of 2003, he had cough and minimal fever and was found to have an abnormal shadow (consolidation in the right upper lobe of the lung) on the chest radiograph. He was admitted to our hospital with bacterial pneumonia on November 26, 2003. He had had oral PSL (daily dose 22.5 mg), and his serum creatinine level was 2.14 mg/dl. He was treated with intravenous meropenem (0.5 g q12h) and oral azithromycin (500 mg per day for 3 days). When his symptoms and fever were improved on December 1, oral levofloxacin (200 mg once a day) was continued for an additional 10 days, and he was discharged on December 10, 2003.

A few days after discharge, he experienced discomfort and pain in both ankles. On December 19, when he stood up

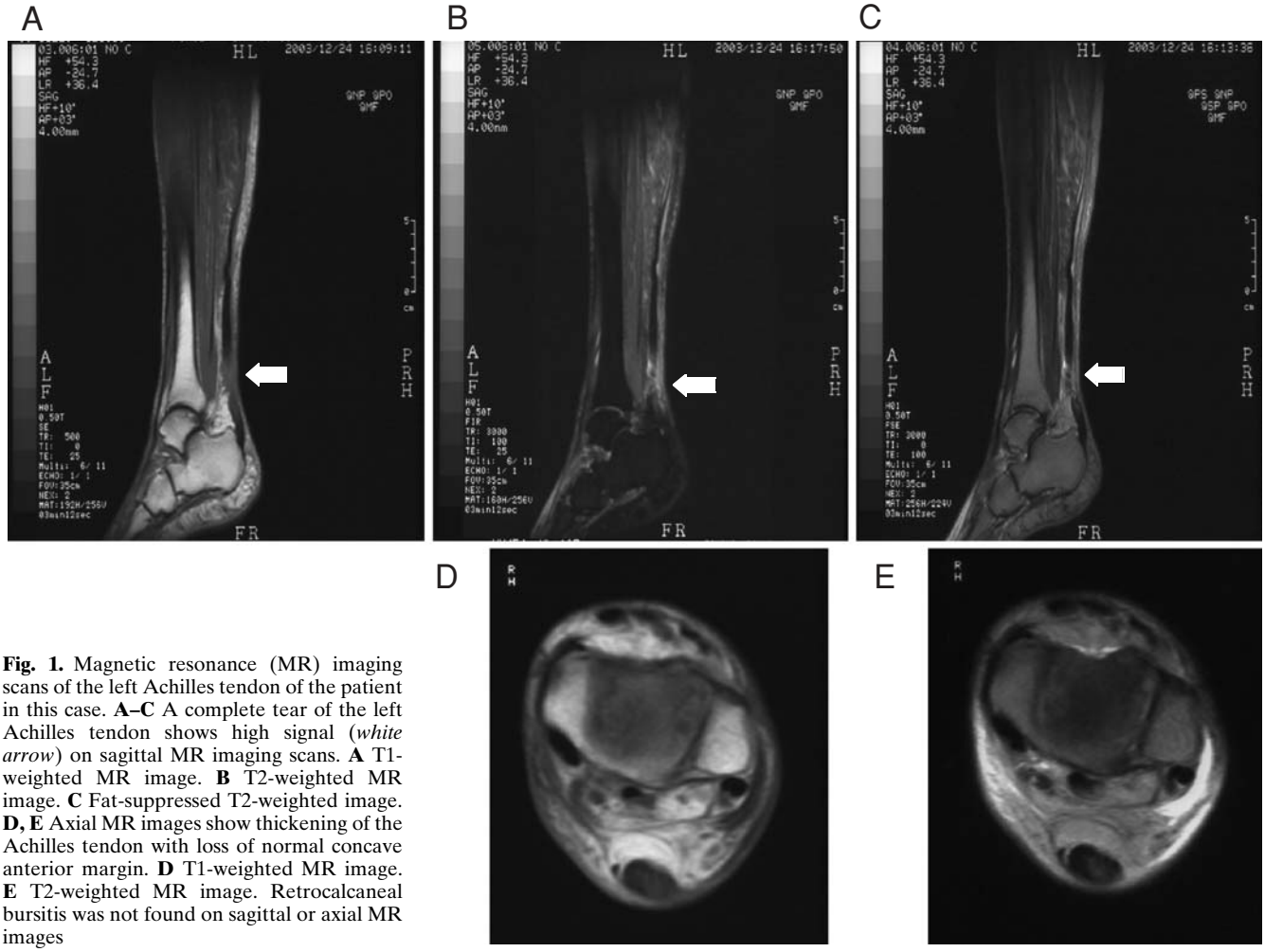

Fig. 1. Magnetic resonance (MR) imaging scans of the left Achilles tendon of the patient in this case. **A–C** A complete tear of the left Achilles tendon shows high signal (*white arrow*) on sagittal MR imaging scans. **A** T1-weighted MR image. **B** T2-weighted MR image. **C** Fat-suppressed T2-weighted image. **D, E** Axial MR images show thickening of the Achilles tendon with loss of normal concave anterior margin. **D** T1-weighted MR image. **E** T2-weighted MR image. Retrocalcaneal bursitis was not found on sagittal or axial MR images

he heard an abnormal sound at his left ankle. The pain at the left ankle then suddenly resolved, but gait disturbance appeared. On December 23, he was seen at a regular appointment. On physical examination, there was swelling and subcutaneous bleeding around his left ankle joint. Mild tenderness was observed in the right Achilles tendon. Thomson's squeeze test was positive for his left foot, and magnetic resonance imaging (MRI) revealed complete tearing of the left Achilles tendon (Fig. 1), indicating that he had bilateral Achilles tendinitis with left Achilles tendon rupture. Because he was not considered a good surgical candidate and he had renal dysfunction and COPD, an ankle-foot orthosis was applied. Several weeks later the abnormal sensation and pain around the right ankle had disappeared. He also received regular physical therapy at a local hospital. He could walk well with the orthosis, but he still experienced discomfort around the left ankle as of December 2004.

Discussion

This patient had spontaneous Achilles tendon rupture associated with systemic microscopic polyangiitis treated with an oral steroid. Several days after 10 days of therapy with levofloxacin he experienced discomfort around both Achilles tendons, which progressed to tendon rupture. Therefore, we diagnosed bilateral Achilles tendinitis with spontaneous rupture induced by levofloxacin.

Fluoroquinolones have been associated with tendon disorders such as Achilles tendinitis and rupture since their introduction during the mid-1980s. Achilles tendon rupture induced by ciprofloxacin was first reported in 1983.[8] During the last decade the number of case reports has increased because of the increased usage of fluoroquinolones.[5,6] The fluoroquinolone-induced tendon disorders usually have an abrupt onset, manifesting as sharp pain while walking, palpitations, or both. Although most tendon disorders have been reported to occur within 1 month after starting a 7- or 10-day course of fluoroquinolone treatment, they can occur as early as a few hours after the initial dose or up to 6 months after drug therapy.[6,7,9]

The relation between fluoroquinolones and tendon disorders, however, is not well understood. Recently, several etiological reports have documented the positive relation between them.[9,10] A case-control study of more than 46000 users of fluoroquinolones conducted in The Netherlands identified 704 fluoroquinolone-treated patients with

Achilles tendinitis, 38 of whom had Achilles tendon rupture. The relative risk of tendon disorders attributable to fluoroquinolone use was 1.9 (95% confidence interval 1.3–2.6), and the excess risk among patients treated with fluoroquinolones was approximately 3 cases per 1000 patient-years of exposure.[10] Another population-based case-control study conducted in the United Kingdom showed similar results.[9]

Moreover, an experimental study using juvenile rats showed that high doses of prefloxacin and ofloxacin caused tendinitis.[11] Williams et al. reported that incubation of canine Achilles tendon fibroblasts with ciprofloxacin significantly decreased cell proliferation compared with that of control cells, and that ciprofloxacin also stimulated matrix protease activity from fibroblasts,[12] suggesting direct toxicity of fluoroquinolones to tendon tissue. Further studies are required to confirm this relation.

The incidence of tendon disorders induced by fluoroquinolones in Japan is unknown, and there are few Japanese reports.[13] To date, fewer than 10 case reports have been published in the Japanese literature. We do not know that this side effect is less common in Japan than in other countries. The standard dosage of fluoroquinolones is lower in Japan than in other countries: the dosage of levofloxacin, for example, is 300 mg per day in Japan and 500–1000 mg per day in other countries. This lower dosage might be one reason for the smaller number of cases reported in Japan. However, the patient described herein received only 200 mg of levofloxacin per day; thus, there is a possibility that its occurrence is underestimated in Japan.

Nontraumatic rupture of the Achilles tendon is rare. The potential risk factors for this condition that have been reported include a history of organ transplantation, renal failure, hemodialysis, rheumatoid arthritis, diabetes mellitus, and systemic corticosteroid use.[10,14] Furthermore, as van der Linden et al. reported, the risk of fluoroquinolone-related tendon rupture is highest among patients over the age of 60 years receiving corticosteroid.[9] Our patient had several risk factors, including advanced age, renal dysfunction, and steroid therapy. Ischemic factors are thought to play a role in the tendon disorders associated with fluoroquinolones, as necrosis with neovascularization, interstitial edema, and degenerative lesions without inflammatory cell infiltration have been demonstrated in pathology studies.[6,7] As in our case, therefore, systemic vasculitis might cause the ischemic changes in the Achilles tendon; this change also contributes to progression to the tendon rupture induced by fluoroquinolones. The MRI scans of our patient show a thickened Achilles tendon, suggesting that hypoxic degeneration might occur in the tendon.[15] Indeed, there are reported the cases of Achilles tendon rupture associated with fluoroquinolones that developed as complications in patients with systemic autoimmune vascular diseases, such as polyarteritis nodosa and systemic sclerosis.[16,17] To our knowledge, ours is the first report of tendon disorders related to fluoroquinolone usage in a patient with MPO-ANCA-related microscopic polyangiitis. Epidemiological studies are needed to confirm the role of systemic autoimmune diseases in tendon disorders.

This rare side effect of fluoroquinolone usage is a serious condition that may lead to significant morbidity and often requires surgical treatment. Thus, physicians should be aware of this adverse effect, especially when prescribing fluoroquinolones for aged patients being treated with corticosteroids.

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