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CASE REPORT

Spontaneous bilateral Achilles tendon rupture in a patient treated with oral levofloxacin

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Abstract A case of bilateral rupture of the Achilles tendon in a patient treated with levofloxacin for cystitis is reported. A 76-year-old woman suddenly developed painful ankles one day after levofloxacin treatment. Drug therapy was switched to amoxicillin/clavulanate on the fourth day. Sonography revealed a serious condition of tendinosis with complete bilateral full-thickness rupture on day 6. Tendons were both repaired in the same surgical session. Pathological anatomy of the specimens reported fatty tissue lobules with panniculitis and histiocytosis. Ankles were immobilized postoperatively with a plaster cast. Achilles tendon rupture may occur as an adverse side effect of short-term use of levofloxacin, a fluoroquinolone antibiotic. This adverse effect is a rare and poorly understood complication of this antibiotic therapy. A review of the literature is provided.

Key words Fluoroquinolone · Levofloxacin · Antibiotic · Achilles tendon · Tendon rupture · Tendinosis · Cystitis

Introduction

Fluoroquinolones are effective antibiotics for the treatment of infections of the upper and lower respiratory tract, urinary tract, skin [1] and eye [2]. Fluoroquinolones are often chosen for their excellent gastrointestinal absorption, superior tissue penetration and broad-spectrum activity [3,4]. Reported adverse effects include nausea, headache, diarrhea, giddiness, abdominal discomfort,

vomiting, agitation, sleep disturbance, rash and pruritis [5]. Other rare but reported side effect are Achilles tendinitis and tendon rupture [3, 6–15] especially in patients 60 years and older [2]. We describe the case of a woman who suffered complete and sudden rupture of both Achilles tendons induced by levofloxacin, an antibiotic of the fluoroquinolones group.

Case report

A 76-year-old woman, currently being treated for hypertension with enalapril who had a deep venous thrombosis four years prior, required antibiotic therapy for cystitis. In November 2006, the patient was prescribed oral levofloxacin (500 mg once daily), each morning, for five days. After just a single dose of this antibiotic, she reported pain in the ankles and difficulty walking. Before the fourth dose of levofloxacin, her family doctor changed the treatment to amoxicillin/clavulanate (1000 mg twice a day). After six days of pharmacological therapy, while the patient attempted to stand up from her sofa, she heard a "crack" sound from both ankles (more intensely from the left ankle) following which she fell to the floor and was unable to rise again. She presented to the Accident and Emergency Department of the Civil Hospital of Iseo (Brescia, Italy) and was admitted to the Orthopaedics and Traumatology Department.

Clinical examination failed to reveal any sign of hematoma on either Achilles tendons (Fig. 1), however the patient demonstrated a positive Thompson sign on both calf tendons. On the following day, sonography and color Doppler sonography of both Achilles tendons were performed. Sonography revealed a serious condition of tendinosis, rich in myxoid degeneration, with complete bilateral full-thickness rupture. Sonography also revealed the presence of abundant hypoechoic sheets put internally the lesion, pointing out a previous subtotal lesion, recently damaged again after trauma, involving full-thickness the tendons. Color Doppler sonography did not reveal any present thrombosis. More importantly, sonography did not report any inflammatory swelling of the surrounding tissues.

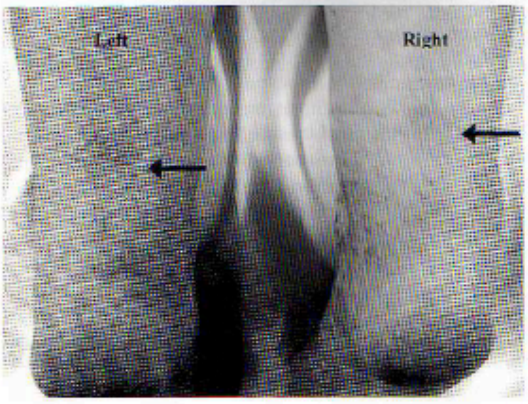

Fig. 1 Photograph of the ankles of a 76-year-old woman who suffered bilateral Achilles tendon rupture (prone position). No sign of hematoma is visible. *Arrows*, cutaneous trace left by the examiner's finger, like a "fovea sign" corresponding to the tendon lesions

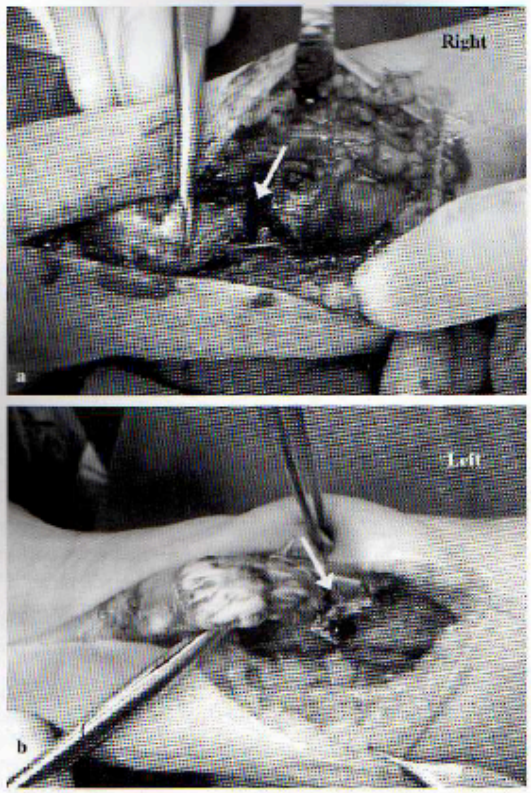

Fig. 2a, b *Complete rupture of the Achilles tendons*. **a** Left tendon. As discovered using sonography, there was remarkable retraction of the rupture ends (*arrow*). **b** Right tendon. As discovered using sonography, there was little diastasis between the rupture ends

Surgical intervention occurred the next day. The intraoperative findings showed complete rupture at the midportion of the Achilles tendons. The left tendon presented a larger gap (Fig. 2a) compared to the right tendon (Fig. 2b). Histological examination of samples retrieved from both tendons, performed by the Department of Pathological

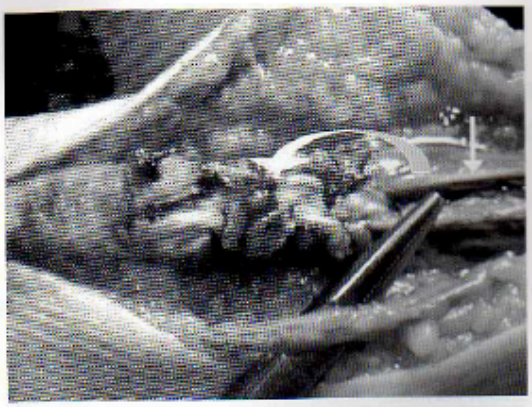

Fig. 3 The Achilles tendon ends were sutured and a patch of proximal end tendon (*straight arrow*), overturned 180° (*curved arrow*), was sutured on the distal end. Fibrin glue was injected into the sutured ends. The sural nerve is visible

Anatomy of Chiari (Brescia, Italy), reported fatty tissue lobules with panniculitis and histiocytosis. A fragment of muscular tissue attached to one tendon specimen showed partial necrosis and the tendon sheath possessed fibrin and chronic inflammation.

An 'end to end' tendon suture was performed bilaterally, which was augmented with a tendon patch (rotated 180°) harvested from the proximal end of the tendon (Fig. 3) to add collagen to the repair site and to enhance biomechanical stability [16]. Finally fibrin glue was injected into the repair site. The operated limbs were immobilized with an above-knee plaster cast with the ankle in maximal plantar flexion for 30 days, following which the cast was replaced with a 90° ankle flexion below-knee plaster cast for a further 30 days. As of January 2007 the cast has been removed and the patient has been ambulatory with progressive weight-bearing, suggesting a good outcome.

Discussion

There are many proposed mechanisms to explain Achilles tendinitis and rupture following fluoroquinolone therapy. Known risk factors and diseases that cause fragility of the tendons include advanced age (60 years and older), systemic lupus erythematosus, gout, chronic renal failure, rheumatic fever, hyperparathyroidism, hyperlipidemia type 2, syphilis, gonorrhea, tumors, rheumatoid arthritis [3, 11, 17–21] and multiple sclerosis (due to chronic corticosteroid therapy) [22]. Hypercholesterolemia associated with hypothyroidism may also contribute to delayed healing and ultimate failure of the degenerated Achilles tendon [23]. In this case, our patient was treated for hypertension but was not taking corticosteroids. Obesity may also predispose to Achilles tendon rupture by both being a marker of sedentary lifestyle that leads to tendon atrophy and increasing periodic strain on the tendon [24]. The heavy mechanical workload of the Achilles tendon (i.e. during weight-bearing activities like walking and running) [11] is also cited as another predisposing factor [7], making the Achilles tendon more vulnerable than other tendons [11].

The relationship between fluoroquinolones (norfloxacin) and Achilles tendinitis was first described by Bailey et al. [25] in 1983. The first described cases of fluoroquinolone-induced Achilles tendon rupture were reported by McEwan and Davey [26] in 1988 regarding ciprofloxacin, followed by Perrot et al. [27] and by Franck et al. [28] in 1991 regarding pefloxacin. According to Karch and Lasagna's algorithm for causality [29, 30] in order to establish a causative connection between the undesirable outcome of a medicine and the suspected medicine, we show that our case report fulfils the appropriate requirement: (a) a reasonable time has passed between taking the medicine and the happening of the event (the sudden onset of tendinopathy after a single dose of a fluoroquinolone suggests a direct toxic effect on collagen fibers) [31], (b) the reaction due to the use of levofloxacin (i.e. a fluoroquinolone) is well known and reported in literature, (c) other possible causes (e.g. traumatism, rheumatoid arthritis, systemic lupus erythematosus, use of corticosteroids, and tendon fragility due to advanced age) were excluded, and (d) symptoms got better when levofloxacin was stopped. Nevertheless, in fluoroquinolone-induced tendinopathy, the tendon can rupture even after these antibiotics are no longer administered [1]. This may explain why in this case both Achilles tendons ruptured during amoxicillin/clavulanate therapy.

A review of the literature conducted by Khaliq and Zhanel [32] illustrated that the first intervention in case of pain includes discontinuation of the implicated fluoroquinolone. Moreover, these authors suggested that the fluoroquinolones most commonly implicated are pefloxacin (37% of the drug-induced tendon injuries) and ciprofloxacin (25.5% of the drug-induced tendon injuries) and that patients with a mean age of 59 years are more susceptible to experience tendon injuries when receiving fluoroquinolones. Therefore, the case we describe is concordant with this review of the literature.

Quinolones have an important affinity for connective tissues [33]. There is a preference for the Achilles tendon, but also shoulder (supraspinatus tendon and long head of biceps), hand (extensor pollicis longus) and epicondylar tendon involvement has been reported [4, 13, 20, 34–38].

Jorgensen et al. [39] proposed that tendon rupture could be the result of a vasculitic phenomenon leading to ischemia. These histological changes due to the cytotoxic effect of these antibiotics on tenocytes could result in a decreased tensile capacity of the tendon and rupture during normal activities [40]. According to Khaliq and Zharel [32], the diagnosis of Achilles tendons rupture is made by physical examination plus sonography and a color Doppler sonography. Cellular death due to the overproduction of free oxygen radicals during fluoroquinolone administration has been reported [2]. Nevertheless, the specific pathophysiology of fluoroquinolone-induced tendinitis and tendon rupture is poorly understood [8]. The absence of hematoma and swelling in both the ruptured Achilles tendons of this case supports the hypothesis that tendon failure resulted from physiological degeneration of the tendons exacerbated by levofloxacin administration. Therefore, elderly patients who are administered levofloxacin should be closely monitored for symptoms of tendonitis [41].

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