



# Quinolones and Tendon Ruptures

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**ABSTRACT:** We report two cases of tendon rupture associated with ciprofloxacin. One patient had a complete rupture of an Achilles tendon 6 months after taking the medication. The other case involved a partial rupture of the subscapularis tendon. Both ruptures occurred with minimal mechanical stress on the tendons, suggesting that the fluoroquinolone increased the susceptibility to rupture. We also review the literature describing the association between fluoroquinolones and tendon rupture and discuss the mechanisms explaining the heightened risk of tendon rupture associated with these drugs.

FLUROQUINOLONES are antibiotics widely used to treat infections in adults. Because immature animals of various species have developed disruption, including erosions, of cartilage after administration of fluoroquinolones, these antimicrobials usually have been avoided in children.<sup>1,3</sup> Disruptions of tendons in adults, including rupture, have been reported in association with fluoroquinolones. The Achilles tendon is the site most frequently associated with such adverse outcomes.<sup>4,5</sup> Typically, fluoroquinolone-associated tendon symptoms, including rupture, occur within the first few weeks after therapy is started.<sup>4,5</sup>

We report two cases of tendon rupture associated with ciprofloxacin that highlight unusual features of this association. One case involves a complete Achilles tendon rupture occurring 6 months after the medication had been discontinued. In the second case, a partial rupture of the subscapularis tendon of the right shoulder occurred during mild stretching exercises. These cases provide insights into the broad nature of tendon ruptures that can be associated with fluoroquinolones. Because these antimicrobials are used commonly, clinicians need to be aware of the potential adverse effects that fluoroquinolones may have on tendons.

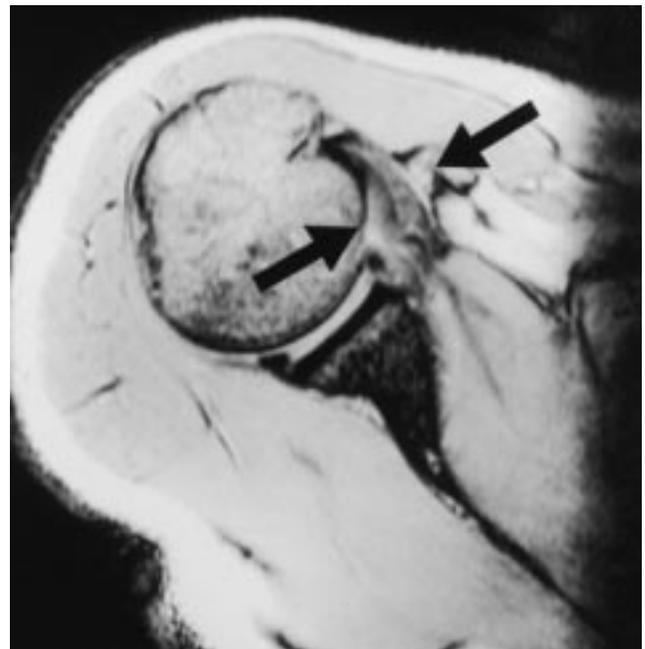
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## CASE REPORTS

**Case 1.** A 38-year-old physician was involved in a motor vehicle accident resulting in vertebral and rib fractures, as well as bilateral hemopneumothoraces. After a 3-week admission, he was discharged on a 1-week course of ciprofloxacin (500 mg twice daily) because of a productive cough. The patient had no symptoms related to his legs until 6 months after discharge. At that time, he had sudden, severe pain while taking a short walk. Physical examination was consistent with a complete rupture of the Achilles tendon. He subsequently had surgical repair of the rupture, with an uneventful postoperative course.

**Case 2.** A 54-year-old physician was given a 10-week course of ciprofloxacin (500 mg bid) for recurrent bacterial prostatitis. Two months into the course, he had marked



Transaxial image of right shoulder shows thickening and increased signal in subscapularis tendon (arrows).

right anterior shoulder pain associated with vertical “push-ups” done against a wall for the purpose of calf muscle stretching. Cessation of the activity and use of nonsteroidal anti-inflammatory drugs (NSAIDs) did not relieve the symptoms. Magnetic resonance imaging (MRI) of the right shoulder showed a partial tear of the subscapularis tendon (Figure). Discontinuing ciprofloxacin, along with starting physical therapy and NSAIDs, completely resolved the patient’s symptoms in 5 weeks.

## DISCUSSION

Classic risk factors for spontaneous rupture of tendons include steroid therapy, hypercholesterolemia, gout, rheumatoid arthritis, advanced age, long-term dialysis, and renal transplantation.<sup>1,6-9</sup> Since 1983, fluoroquinolones have also been reported to be associated with disruption of tendons.<sup>7,9,10</sup>

Tendon disorders associated with fluoroquinolones have been estimated to occur at a rate of approximately 15 to 20 per 100,000 patients.<sup>11</sup> Fluoroquinolone-associated tendinitis most commonly involves the Achilles tendon, but the quadriceps, peroneus brevis, extensor pollicis longus, the long head of the biceps, and rotator cuff tendons have also been reported.<sup>7,11</sup>

In one series of 100 cases of fluoroquinolone-associated tendon disorders, the Achilles tendon was involved in 96 cases, with almost half of these cases having bilateral involvement.<sup>4</sup> Tendon rupture occurred in 31% and tendinitis in 69%.<sup>4,5</sup> The average time between the start of treatment to the onset of symptoms was 13 days, with a range of 1 to 90 days.<sup>4,7</sup> Among the 25 cases of fluoroquinolone-associated Achilles tendon rupture reported to the Food and Drug Administration (FDA) by 1994, 16 had associated risk factors such as advanced age, renal failure, or corticosteroid use.<sup>2</sup> Although tendon rupture in one series occurred within 2 weeks of starting antibiotics in half of the cases, rupture may occur after discontinuing the offending medication.<sup>7</sup>

Magnetic resonance imaging can be a useful means of diagnosing rupture of a tendon, and even tendinitis.<sup>5,11,12</sup> Even with early diagnosis and management, discontinuance of the fluoroquinolone, and placement of the tendons at rest, tendinitis heals slowly.<sup>11</sup> One study found that only 50% of patients with fluoroquinolone-induced tendinitis recovered in 1 month.<sup>11</sup> In another study, 25% of the patients had symptoms that persisted for at least 2 months.<sup>7</sup>

According to reports from France, which has an aggressive drug side-effect monitoring program, fluoroquinolones associated with tendon ruptures include, in descending order of asso-

ciation, pefloxacin, ofloxacin, norfloxacin, and ciprofloxacin. The risk associated with pefloxacin has been estimated to be 1 case per 23,130 treatment days, and for ciprofloxacin, 1 case per 779,600 treatment days.<sup>13</sup>

There have been three reports of patients with fluoroquinolone-associated disruption of the Achilles tendon in which histopathology was obtained. In one patient who had a rupture, the histopathology showed necrosis along with neovascularization, multiple fissures, and interstitial edema, but no inflammatory cell infiltrate.<sup>4,11</sup> Histopathology in a second case of ruptured Achilles tendon showed necrosis and cystic changes that are not found in non-drug-associated tendinopathies.<sup>14</sup> Another patient had pain and swelling of one Achilles tendon 9 months after only a 1-week course of ciprofloxacin (500 mg bid). Biopsy of the tendon was done 4 months after the onset of symptoms. Histologic examination revealed abnormal fiber arrangement and structure with fibrotic areas, hypercellularity with some nuclei being more rounded, neovascularization, and increased glycosaminoglycans in the extracellular matrix.<sup>4</sup> These histologic findings are similar to those in tendon overuse injuries in athletes.<sup>4</sup>

Further support for a causal effect of fluoroquinolones on tendons comes from an animal model. One day after juvenile rats were given a single dose of ofloxacin and pefloxacin, their Achilles tendons showed alterations of the collagen, edema, and an inflammatory infiltrate.<sup>4</sup> After administration of the fluoroquinolone for 2 weeks, the inflammation had subsided, and regenerated fibroblasts with foci of fibrosis were found, consistent with a healing process after the resolution of fluoroquinolone-induced inflammation.<sup>4</sup>

It can be difficult to prove cause-and-effect relationships involving medications and certain side effects. This is particularly true in untoward effects such as tendon ruptures, which may occur in the absence of any medication, particularly since the reported cases frequently had coexisting risk factors.<sup>15</sup> However, clinical reports, histopathologic findings, and an experimental model support a causal relationship between fluoroquinolone use and tendon ruptures.

Since it is often difficult to establish causality for individual cases, efforts to quantify the risk of tendon ruptures should be viewed as only estimates.<sup>7</sup> There may be a bias in overreporting an association between tendon rupture and fluoroquinolone use, involving cases that might

have spontaneously occurred without the medication. On the other hand, the association may be unrecognized, and therefore some cases may be underreported.<sup>6,7</sup> If the MRI had not been taken in the patient complaining of shoulder pain, the partial tear of the subscapularis tendon might have been missed. Furthermore, tendon disruption may occur months after initiating treatment with a fluoroquinolone, and an association may not be considered. Previous reports indicate that onset of symptomatic tendon disruptions may be delayed for 90 days after starting the antibiotic.<sup>7,11</sup> Another case report described an individual who had 9 months of symptoms after a 1-week course of fluoroquinolones.<sup>4</sup> The histopathology in this patient is particularly noteworthy. Abnormal biopsy findings, consistent with a reactive healing process, were found at 4 months, suggesting these medications may have prolonged effects on tendons.<sup>4</sup> The presence of a cystic change in another patient<sup>14</sup> suggests the pathophysiologic changes associated with fluoroquinolones may not be completely reversible, at least in some cases. The prolonged symptoms associated with increased glycosaminoglycans of the tendon in one patient who had only a 1-week course of antibiotics<sup>4</sup> and the cystic changes in another patient<sup>14</sup> support mechanisms for ruptures to occur long after the antibiotic therapy has been discontinued.

An abnormal reactive healing response, or cystic degeneration, may be responsible for our case of the rupture that occurred 6 months after ciprofloxacin therapy was discontinued. Changes in cellular function induced by fluoroquinolones, similar to those seen in tendon overuse conditions, are associated with increased glycosaminoglycans.<sup>4</sup> Such changes may predispose tendons to rupture, just as could be expected for cystic degeneration.

The high proportion of Achilles tendon involvement associated with fluoroquinolones is probably related to mechanical forces,<sup>11</sup> and possibly to vascular factors.<sup>7</sup> However, as one of our cases illustrates, rupture of tendons other than the Achilles may be associated with fluoroquinolone use. Neither of our patients had other risk factors for tendon rupture, corroborating the FDA series in which slightly more than one third of patients lacked coexisting risk factors.<sup>2</sup>

Our cases add to the anecdotal evidence suggesting a causal relationship between fluoroquinolones and tendon rupture. Additionally, these cases highlight the broad nature of ten-

don ruptures that may be associated with this class of medications. Tendons other than the Achilles may be affected by the use of fluoroquinolones. Furthermore, a considerable delay may exist between the administration of a fluoroquinolone and the spontaneous rupture of a tendon. In one of our cases, the delay was 6 months after completion of a course of ciprofloxacin. However, evidence from previous reports suggests that such a delay is possible. The rat model shows that fluoroquinolones may produce inflammation of the tendon within 1 day after their administration.<sup>4</sup> An abnormal healing response to fluoroquinolone-associated inflammation,<sup>4</sup> or cystic degeneration<sup>14</sup> may produce effects months after completion of even a short course of a fluoroquinolone.

## CONCLUSION

Fluoroquinolone-associated tendon disruption, including rupture, is well described in the literature. Although the Achilles tendon is the most susceptible site, other tendons may be affected. Typically, spontaneous tendon rupture occurs during or shortly after a course of therapy, but symptoms may occur months after taking fluoroquinolones. Whether fluoroquinolones should be used in patients with a history of tendon problems or with risk factors for the development of tendon ruptures depends on the seriousness of the infection and the alternatives available. Awareness of the association between tendon disorders and fluoroquinolones may lead to enhanced surveillance, which should be extended to sites beyond the Achilles tendon and to periods of months after a course of these antibiotics.

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See also page 525.