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Peroneal longus tendon rupture after fluoroquinolone therapy: A case study

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Fluoroquinolones are a class of antibiotics that are commonly used to treat gram-negative and gram-positive bacterial infections. Tendinopathies, most commonly affecting the Achilles tendon, are a possible side effect with the use of Fluoroquinolones. Tendinopathies may occur from two hours to six months upon starting a course of fluoroquinolones. This case study presents a patient who had a magnetic resonance imaging (MRI) confirmed peroneus longus tendon rupture with the presence of an os peroneum fracture after two courses of ciprofloxacin treatment, one course five months prior to the injury and the second course one month prior to the injury. Physicians and patients should monitor for tendon soreness and pain in the peroneus longus tendon in addition to the classically documented Achilles tendon following the use of fluoroquinolones.

Keywords: fluoroquinolone, ciprofloxacin, tendinopathies, peroneus longus, peroneus longus tear, tendon rupture

A 45-year-old morbidly obese male presented with a complaint of severe pain to the lateral aspect of his left foot lasting for over three weeks. The patient stated he was walking on uneven terrain in his backyard prior to the onset of pain. He did not relate a specific injury but after 15 minutes of yard work, noticed increased pain. The pain was reported on the lateral aspect of the left foot at the fifth metatarsal base and cuboid. He stopped his activity and applied an over-the-counter ankle support sock, along with ice and rest. He started himself on an anti-inflammatory course of Naprosyn 500mg twice a day with food. The patient's previous medical history includes asthma, hypertension, and pre-diabetes. His last hemoglobin A1c (HbA1c) prior to this incident was 5.9%. The patient denied all pertinent medical and surgical history.

After a thorough physical exam with noticeable swelling and pain at the calcaneocuboid joint, three standard radiograph views, anteroposterior, medial oblique and lateral, were taken of the left foot (Figures 1, 2, and 3). Significant osteoarthritic changes including osteoarthritis at the talonavicular joint and the calcaneal cuboid joint were noted along with both plantar and retrocalcaneal spurring. An os peroneum at the peroneal groove was noted. There were no acute fracture patterns noted. The patient was treated conservatively for a left foot sprain. The patient was dispensed an ankle stabilizing orthosis (ASO) brace with straps and was given a continuation of anti-inflammatory Naprosyn 500mg twice daily for two weeks and told to follow the rest, ice, compression, and elevation (RICE) protocol and reduce his activity to as tolerated.

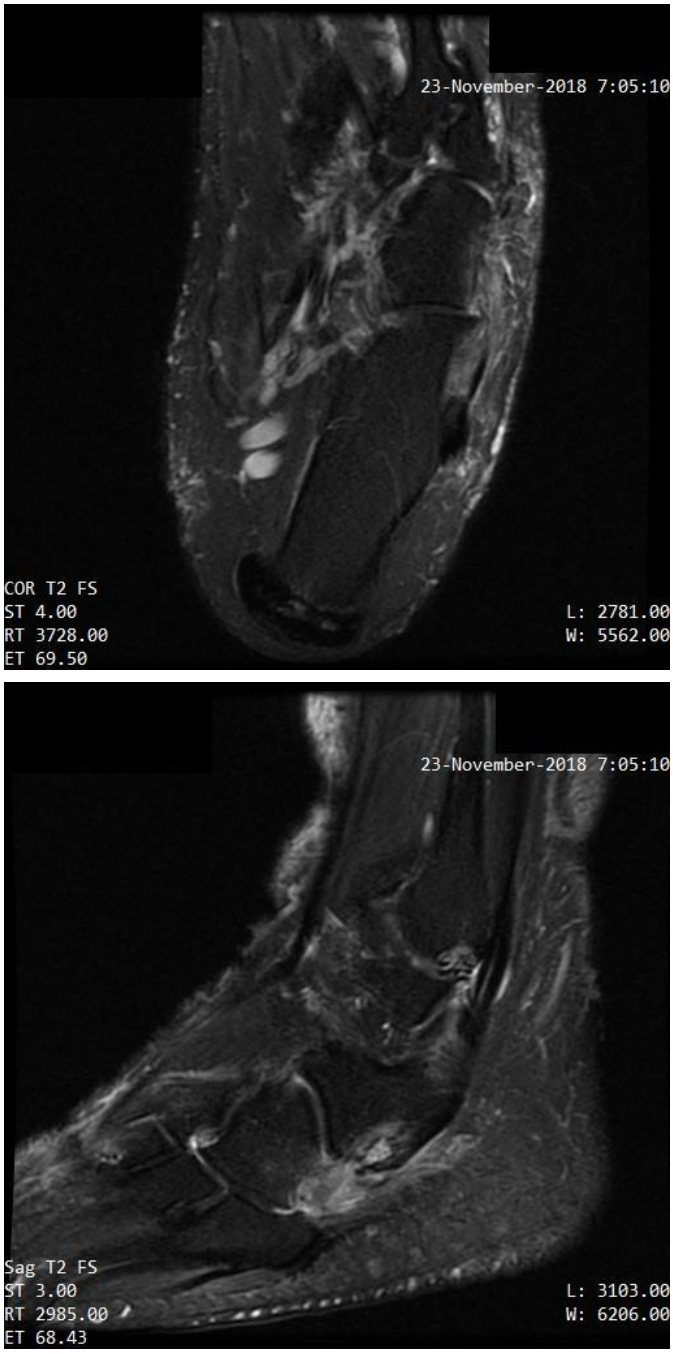
Four days after the initial visit the patient was ambulating to his car when there was an audible "pop" with immediate pain and swelling in the left foot. The patient reported an inability to ambulate without significant pain. The next day the patient returned to the clinic and new radiographs standard three views were taken of the left foot (Figures 4, 5, and 6).

Figures 1, 2, and 3 Three standard radiographic weight-bearing views of the left foot. Anteroposterior, lateral, and lateral. Initial office visit, prior to rupture. Incidental findings of phleboliths noted to the lower leg consistent with venous stasis.

A fleck-fracture was noted at the posterior plantar aspect of the cuboid. The os peroneum was translocated proximally and was no longer noted in the peroneal groove as compared to previous radiographs. There was joint space narrowing and edema noted at the level of the midfoot. The lower extremity physical examination revealed there was severe tenderness and pain on palpation at the lateral aspect of the fifth metatarsal base, cuboid, and peroneal tendon at the level of the cuboid. There was mild edema noted on the base of the fifth metatarsal base.

Figures 4, 5, and 6 Three standard radiographic weight-bearing views of the left foot. Anteroposterior, lateral, and medial oblique. Second office visit, following rupture.

The differentials at the visit were peroneus longus tear (partial versus complete) and fleck-fracture of the cuboid. The patient was treated conservatively for the pain and ordered to undergo an MRI without contrast to determine if there was a peroneus longus tear. The patient was recommended over-the-counter nonsteroidal anti-inflammatory drugs (NSAIDs) and instructed to follow a rest, ice, compression, elevation (RICE) protocol at night to reduce inflammation. Due to the patient's large body habitus, he was unable to remain completely non-weight bearing. The patient was prescribed a controlled ankle motion (CAM) walker to protect structural alignment and to absorb shock during weight-bearing.



Figures 7 and 8 T2 Coronal and T2 Sagittal ankle MRI without contrast, 3 weeks post-injury, showing a complete tear of the peroneus longus tendon at the level of the calcaneocuboid joint, measuring two centimeters, which is filled with soft tissue edema.

The patient completed the MRI study three weeks later (Figures 7 and 8). Which demonstrated a complete tear of the peroneus longus tendon at the level of the calcaneocuboid joint. The defect of the tear measured two centimeters and was filled with soft tissue edema. There were thickening and small cystic changes noted at the edge of the proximal portion of the torn tendon. The distal attachment of the torn tendon at the first metatarsal base was intact. The peroneus brevis tendon was intact. There was mild peroneal tenosynovitis noted. There was no acute fracture or osteonecrosis noted. There was no focal osseous lesion noted. There was mild tenosynovitis of the flexor hallucis longus tendon at the master knot of Henry. There was Achilles tendinosis and interstitial insertional partial tearing noted. Retrocalcaneal bursitis was also noted.

Upon further questioning, five months prior to this injury the patient was on a course of ciprofloxacin 500 mg twice daily for seven days prescribed and completed for an upper respiratory infection. One month prior to this injury the patient was prescribed half a course of ciprofloxacin 500 mg twice daily prescribed for an upper respiratory infection but the course was discontinued due to gastrointestinal (GI) complications. Surgical discussion ensued regarding a primary repair, but the patient declined surgery at the time due to a multitude of factors including the inability to be non-weight bearing and the patient's job requirements. At the time, the patient's current orthotics were modified to include slightly more arch support along the metatarsals and to offload the cuboid. The patient reported back to the clinic two months later with no pain and was back in regular shoe gear.

Discussion

Fluoroquinolones are a class of antibiotics for broad-spectrum use primarily prescribed for infections caused by gram-negative bacteria. First introduced in the 1980s, fluoroquinolones are often prescribed for gastrointestinal and genitourinary tract infections [1,2]. Fluoroquinolones are often prescribed because of their high oral bioavailability and their high penetrance into bones and soft tissue [2,3]. Fluoroquinolones are contraindicated in women during pregnancy due to fetal malformations, in children with open growth plates due to the possibility of cartilage damage and growth disruptions due to the high bone penetrance, and in athletes because of increased risk of tendinopathy [1-3].

As a class, fluoroquinolones are bactericidal by inhibiting bacterial DNA gyrase, preventing DNA replication and cell division [3]. Fluoroquinolones should only affect bacterial cells but can exhibit cytotoxic effects in mammalian musculoskeletal tissue [3]. In a critical review of literature by Khaliq et. al, the most common fluoroquinolones, with reported

tendon injury are perfloxacin and ciprofloxacin, a second-generation fluoroquinolone [1]. The mechanism by which fluoroquinolones result in tendinopathy is not clear. Rodent studies have shown a couple of possible molecular mechanisms. Kato et. al found edema with mononuclear cell infiltration in the tendon sheath of the Achilles tendon and surrounding synovial membranes and joint spaces in rats treated with a single dose of pefloxacin or ofloxacin [4]. The damaged cartilage releases degraded matrix substances that can initiate lesions in the tendon. Ciprofloxacin upregulates the expression of matrix metalloproteinase-2 in tendon cells causing the degradation of type I collagen [5]. Khaliq, et al., showed that ciprofloxacin significantly decreases the proliferation of fibroblasts, synthesis of collagen, and synthesis of proteoglycan [1].

A review by Khaliq, et al., describes documented cases of patients showing symptoms of Achilles tendinopathy as early as two hours after starting a course of fluoroquinolone and as late as six months after the completion of the course of treatment. The median course of fluoroquinolone treatment prior to tendinopathy was eight days. Of a 98 case study, the second most common fluoroquinolone to induce tendinopathy was ciprofloxacin (25.5%) with daily doses 500 mg to 2000 mg [1].

The primary intervention for a patient experiencing tendon soreness or pain secondary to fluoroquinolone use is to decrease the dosage or discontinue the medication. In a case presented by Khaliq, et al., a patient was prescribed Norfloxacin, 400 milligrams twice a day, and experienced symptoms of Achilles tendonitis. The primary intervention in this case was to reduce the dosage to 200 milligrams once a day, which alleviated the symptoms. The patient was then rechallenged to a higher dosage of 400 milligrams twice a day, which resulted in a reoccurrence of the Achilles tendonitis. However, once the dosage was reduced back to 200 milligrams once a day, the symptoms were alleviated [1].

The Achilles tendon is the site of 89.8% of fluoroquinolone-associated tendinopathies and tendon ruptures [3]. Other affected tendons include the biceps brachii, supraspinatus, and extensor pollicis longus [3]. In this case study, a patient treated with ciprofloxacin resulted in a rupture of the peroneus longus tendon, a fleck fracture of the cuboid, and a proximal translocation of the os peroneum.

The peroneus longus tendon is positioned lateral and posterior to the peroneus brevis tendon within the lateral compartment of the leg. The peroneus longus tendon courses on the cuboid groove and inserts onto the plantar aspect of the first metatarsal and the lateral aspect of the medial cuneiform [6]. An accessory bone, os peroneum, is located in the peroneus longus tendon on the plantar lateral aspect of the cuboid as the tendon arches around the cuboid [7]. The os peroneum is present in about 20% of adults and 60% of the time is identified bilaterally [7].

Peroneal tendons have avascular zones in the anatomic region where most tears occur. These avascular zones contribute to pathogenesis and poor healing of the peroneal tendons in these areas [8]. In an immunohistochemical study of cadaver tendons, Peterson, et al., reported that the peroneus brevis has a single avascular zone and the peroneus longus tendon has two avascular zones[8]. The peroneus brevis has an avascular zone where the tendon passes through the fibular groove [8]. The peroneus longus has one avascular zone where the tendon curves around the peroneal trochlea of the calcaneus and another where the tendon wraps around the cuboid [8].

Pierfitte and Royer reported the largest review of tendinopathies and ruptures associated with fluoroquinolone use. Of the four-hundred and twenty-one cases of tendinopathies associated with fluoroquinolone use, ninety-eight percent of the cases occurred in the Achilles tendon [9]. Peroneal brevis tendinopathies and ruptures associated with fluoroquinolone use have been reported to occur, although a rate of occurrence has not been established. After a thorough literature search, a case report identifying the incidence of a peroneus longus tendinopathy or rupture following the use of fluoroquinolones remains obsolete. This case study identifies a peroneus longus rupture following ciprofloxacin use and aims to remind physicians and patients to monitor for symptoms of tendinopathies beyond the most notably reported Achilles tendon. Injury has been reported to occur within hours to months after the initiation of fluoroquinolone therapy and even after completion of the antibiotic [1]. Monitoring for symptoms of tendinopathies and ruptures may extend for over six months.

Generally, in tendinopathy of the peroneal tendons, patients report the gradual onset of pain, swelling, and edema. Often, patients complain of lateral ankle

and foot pain following inversion injuries. In cases of tendon ruptures and dislocations, patients may report snapping sensation during the injury [6].

There are several possible differential diagnoses to be aware of and should be ruled out. A lateral ankle sprain may be ruled out with anterior drawer and talar tilt test. Os trigonum syndrome can be observed under MRI with plantarflexion of the foot. Peroneal subluxation may be determined with an ultrasound, computerized tomography (CT) scan, or MRI study. In cases of lateral foot pain, it is necessary to rule out an os vesalianum, os cuboideum, painful apophysis of the fifth metatarsal, and an avulsion fracture with radiographs.

The associated risk among the general population for fluoroquinolone-induced tendinopathy is low at 0.14-0.4%. There are several risk factors that increase the risk of tendinitis when taking ciprofloxacin. Patients who are older than 60 years of age, patients who are concurrently undergoing systemic corticosteroid therapy, chronic renal failure, hemodialysis, diabetes mellitus, and patients with a history of musculoskeletal disorders. According to Kim, the average age for fluoroquinolone tendinopathy is 64 years old with a 2:1 ratio male-to-female, and 27 percent of patients experienced bilateral tendinopathies. The greater effects of fluoroquinolone-induced tendinopathy occur at higher doses [3].

Diagnostic exams are crucial to identify peroneal tendon rupture with or without an os peroneum fracture. The medial oblique is the best radiographic view to visualize the os peroneum. Displacement of os peroneum is an indirect sign of peroneal tendon rupture. The gold standard diagnostic imaging for peroneal tendon tear with or without os peroneum is an MRI due to their high sensitivity and specificity rates [6]. The tendon may also be observed under ultrasound in which the tendon is seen as a curved echogenic focus with posterior acoustic shadow.

There are conservative and surgical treatments for fluoroquinolone-induced tendinopathy. Fluoroquinolones should be discontinued for alternative therapies immediately if there is an onset of tendon soreness and pain. In general, peroneal tendonitis without rupture responds well to conservative treatment options such as analgesics, a cast, immobilization, custom orthoses with valgus wedging, or physical therapy [1,6]. Patients may take over-the-counter analgesics such as aspirin, ibuprofen, or naproxen. To help reduce inflammation of the tendon the patient may be placed in a below-knee cast, air cast, splint, or CAM boot for immobilization for four to six weeks. Physical therapy treatment for peroneal tendonitis includes stretching, strengthening, and balancing exercises. Peroneal tendon rupture may require surgical treatments for tendon repair. For patients who have an os peroneum, it may be excised during the operation and the peroneus longus tendon is attached to the peroneus brevis [6].

Conclusion

A side-effect of the antibiotic class of fluoroquinolones is tendinopathy, most commonly affecting the Achilles tendon. Tendinopathies may occur from two hours to six months upon starting a course of fluoroquinolones. The diagnosis of peroneal longus tendinopathy and ruptures requires evaluation and monitoring for tendon soreness and pain. Based on this case study, fluoroquinolone-induced tendinopathy and rupture is not exclusive to the Achilles tendon and requires evaluation of other tendons in the foot, such as the peroneus longus.

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