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Case Report

"Ciprofloxacin-induced" bilateral quadriceps tendon rupture: A case report and conclusions of the recent literature

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ABSTRACT

The potential risk of fluoroquinolones on the musculoskeletal tissue, and tendinous structures in particular, has been known since its introduction in the 1980s. Following reports of serious and persistent side effects in their national registry, the German medicines authority (BfArM) has requested the European Medicines Agency (EMA) to conclude a safety review focusing on long-lasting effects mainly affecting the musculoskeletal and nervous systems. This review, published in early 2019, led to restriction of the usage of fluoroquinolones due to the risk of disabling and potentially long-term side effects. Furthermore, there have been a number of meta-analyses published in the recent years, which brought more clarity to the extent of fluoroquinolones' possible side effects. With this case report followed by an overview of the latest evidence, we would like to highlight these latest efforts in the quest to prescribe fluoroquinolones cautiously and sensitize physicians to this topic.

Case history

A 59-year old male teacher, with no pre-existing medical comorbidities other than hyperplasia of the prostate, presented to our emergency department with inability to walk and pain on the upper margins of his patella on both sides. He reported playing football with some friends, as he suddenly slumped to the ground while trying to pass the ball without any adversary contact. He didn't describe any pain located around his knees before the incident and has neither been treated for any disease nor trauma on his lower limbs. Other than tamsulosin for his prostate hyperplasia, he was on no regular medication. His medical history was significant only for completing a 24-day course of ciprofloxacin for a prostate infection a year before the incident.

On physical examination, swelling was recognized as well as dimples during palpation on top of both kneecaps. He was unable to extend both knees and a positive leg raise test was seen bilaterally. There were no other deficits in power, sensation or proprioception in either lower limb. Knee x-rays showed an unusual contour of the suprapatellar soft tissue bilaterally, with a sagging of both suprapatellar regions, radiographically indicating bilateral quadriceps tendon rupture (Fig. 1). On the right knee, a CT-scan was performed to rule out any osseous lesion, whereby the suspicion of a quadriceps rupture became more concrete. Due to the distinctive clinical presentation of complete tendon rupture bilaterally, no further diagnostics were initiated, and the patient was treated operatively the next day.

Intraoperatively, the clinical findings of complete tears of the quadriceps tendon on both sides were verified. The tear on the left side showed hardly any signs of a fresh tear, but a largely degenerated quadriceps tendon with fraying and fatty streaks within the

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tendon. No inserting fibers were left at the proximal pole of the patella, which led to the assumption that a degenerative, partial tear might have already existed prior to the incident. Also, the proximal part of the ruptured tendon on the right side showed degenerative signs with fraying and fatty strikes, but there were signs of a complete fresh tear with a few freshly ruptured fibers inserting at the proximal pole of the patella. Both tendons were readapted by a hybrid of suture anchors and transosseous tunnel repair technique.

Postoperatively, the patient remained full weight-bearing in extension for six weeks. Unfortunately, within the six weeks post-operatively our patient had an incident in which he slipped away with his right leg on the wet floor of his bathroom. For a couple of days, he felt self-limiting pain in the right leg. On clinical examination 6 weeks postoperatively, a well healing left lower limb could be seen with no extension lag. On the right side, a dimple could be palpated proximal to the patella around the scar, as well as diminished quadriceps contraction was observed. In the subsequently initiated magnetic resonance imaging (MRI) of the right knee, the clinical suspicion of a re-ruptured quadriceps tendon was confirmed.

In the operative revision of the re-ruptured right quadriceps tendon, a torn central suture was seen with a central defect of around 3 cm width and dehiscence of 2 cm. Due to the retraction and impaired quality of the quadriceps tendon, a V—Y plasty was performed with subsequent adaption to the patella by a hybrid of suture anchors and transosseous tunnel repair technique. Postoperative conventional radiographical and computer tomographic findings showed the medial anchor to be placed subchondral, which needed another operative revision with replacement of the aforesaid anchor. Postoperatively, full weight-bearing in extension for six weeks was initiated again.

In the latest outpatient consultation 10 months after surgical treatment on the left and 8 months after the revision surgery on the right quadriceps tendon, a well healing left knee could be observed with normal extension motor strength levels, as well as increasing range of motion (Flexion/Extension 130/0/0°) and no extension-lag. The right knee showed good range of motion (Flexion/Extension 120/0/0°) as well as close to normal extension motor strength levels without any extension-lag, but a persistent dent could be seen and palpated on the superior margin of the patella. The patient described to possess good stability and strength in the left leg, but persistent limited strength levels during climbing stairs and longer walks as well as faster exhaustion with consequent rare instability and giving-way symptomatic on the right side. In regard to these restrictions and the observed suprapatellar dimple, another MRI examination of the right knee was undertaken to assess the integrity of the quadriceps tendon. This MRI showed an intact right quadriceps tendon with elongated and persistent edematous alteration (Fig. 2). In order to address the persistent impaired strength and stability intensive muscular strength-training has been continued.

Discussion

The toxicity of fluoroquinolones on musculoskeletal tissue has been acknowledged since its introduction in the 1980s. In the late 20th and the beginning of the 21st century, there has been a rising number of reported cases of tendon-related issues with this drug class, which has led the Food and Drug Administration (FDA) to add a 'black box' warning to fluoroquinolone antibiotics in 2008 – the most stringent warning there is [1]. Following reports of serious persistent side effects mainly affecting muscles, joints and the nervous system, recently, also the European Medicines Agency (EMA) concluded a safety review of fluoroquinolone antibiotics, which led to

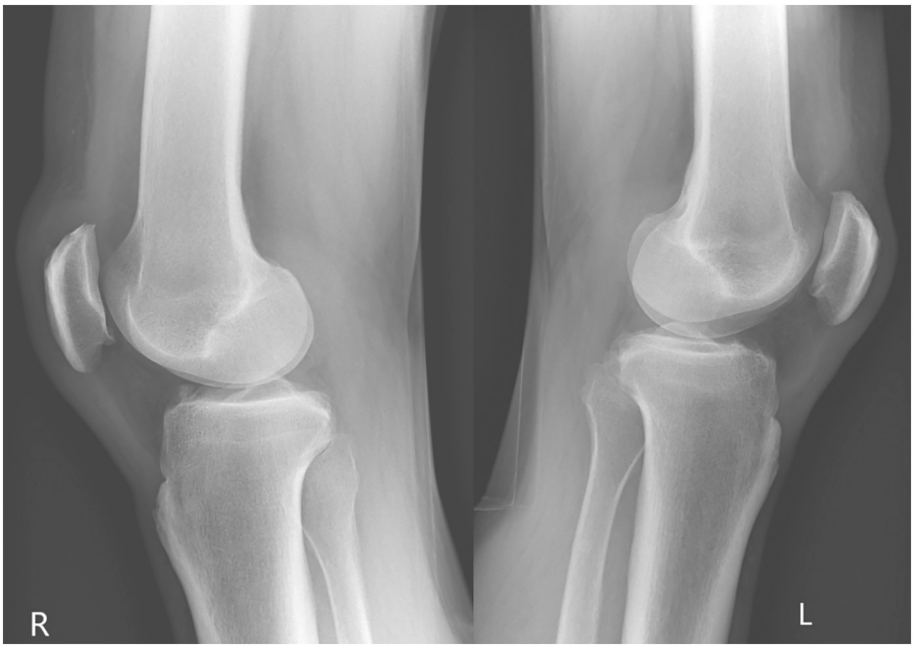

Fig. 1. Bilateral Knee x-rays on the day of the incident.

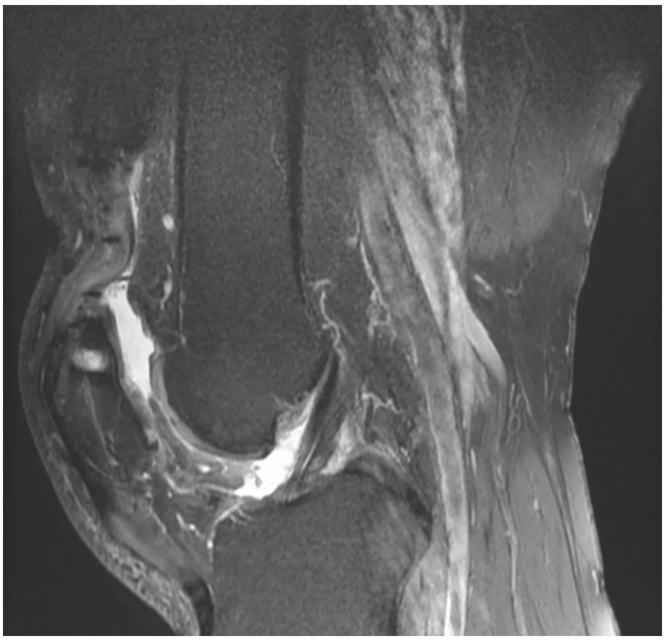

Fig. 2. MRI examination of the right knee 8 months after surgical revision.

restriction of its use due to the risk of disabling and potentially long-term side effects (see Table 1) [2]. Tendinopathy and tendon ruptures after treatment with fluoroquinolones are almost exclusively seen in Achilles tendons [3]. Quadriceps tendon tears associated with fluoroquinolone therapy are hardly ever seen and we only found one other case report about this rare incident [4].

Acute quadriceps tendon rupture is a relatively rare injury (incidence 1.37/100′000), usually seen in middle-aged men [5]. The typical mechanism of injury is an indirect trauma with a violent contraction of the quadriceps muscle with the foot planted on the ground and the knee partially bent [6]. Besides fluoroquinolones, several pre-existing conditions increase the risk of quadriceps rupture such as obesity, systemic lupus erythematosus, rheumatoid arthritis, chronic renal failure, gout, hyperparathyroidism and corticosteroid intake [7]. Shah concludes in his risk analysis of 66 simultaneous, bilateral quadriceps tendon ruptures that younger patients with this injury should be evaluated for any underlying medical condition [8].

In our case, no other risk factor than the intake of ciprofloxacin a year before the incident was apparent. Besides, the relative atraumatic nature of the injury and the intraoperative findings of largely degenerated tendons on both sides imply ciprofloxacin to be the causative agent. The mechanism for fluoroquinolone-induced tendon rupture remains poorly understood but has been linked to the degradation of Type I collagen following alterations in the regulation of matrix metalloproteinases [9]. The resulting symptoms, such as sudden pain, tenderness to palpation, edema and difficulty with movement of the involved area, may appear as soon as 2 hours after first dose of fluoroquinolone. On average, the duration of fluoroquinolone therapy before the onset of tendon injury is 8 days [3]. However, as seen in our case and also stated by the EMA, they can cause long-lasting and potentially permanent side effects involving tendons, muscles and joints [2].

A number of recently published systematic reviews on this topic have underlined the increased risk of tendon injuries associated with fluoroquinolones. While generally spoken the odds ratio for any tendon disorder is roughly doubled after the intake of a fluoroquinolone therapy in the general population, it is of particular interest to identify high-risk populations, as they are at a substantially higher risk for tendon associated disabilities [10,11]. When one is trying to distinguish what patient is at particular risk, three criteria appear to possess a major role: age (>60 years), concomitant intake of corticosteroids and duration of the antibiotic therapy. In absolute measures, for a person under the age of 60 years who is prescribed to 5 days of a fluoroquinolone therapy a number needed to treat (NNT) to cause one additional tendon rupture of 1:521,429 (CI 405,556–730,000) results. Whereas for a person over the age of 60 years with a therapy duration of 28 days and concomitant corticosteroid intake the NNT to cause one additional tendon rupture increases to 1:6651 (CI 5173–8690) [12].

Table 1
Recommendations endorsed by the EMA's human medicines committee (CHMP) on the use of fluoroquinolone antibiotics [4].

Restrictions on the use of fluoroquinolone antibiotics will mean that they should not be used:
• to treat infections that might get better without treatment or are not severe (such as throat infections).
• to treat non-bacterial infections, e.g. non-bacterial (chronic) prostatitis.
• for preventing traveler's diarrhea or recurring lower urinary tract infections (urine infections that do not extend beyond the bladder).
• to treat mild or moderate bacterial infections unless other antibacterial medicines commonly recommended for these infections cannot be used.

According to the FDA, the possible serious side effects of fluoroquinolones (incl. tendinous disorders) generally outweigh the benefits for patients with milder infections (for example acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, and uncomplicated urinary tract infections). Hence, fluoroquinolones should be reserved for these conditions only if no alternative treatment option exists [13]. Despite the aforementioned elevated risk for developing a tendinous disorder, fluoroquinolones are still commonly prescribed for treating milder infections [14].

In conclusion, in keeping with the warnings from the FDA and EMA, we strongly suggest that fluoroquinolones should only be prescribed after careful consideration for alternative treatment options, especially in patients with preexisting risk factors for developing tendinopathy. Furthermore, careful patient instruction regarding possible signs of tendon damage should be carried out when prescribing fluroquinolones.

CRediT authorship contribution statement

All authors contributed to the idea to report the case and had full access to all of the data in the study and take responsibility for the integrity of the data. All authors contributed to patient management. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: CS and RT. Critical revision of the manuscript for important intellectual content: All authors. Clinical case presentation and management undertaken at Zuger Kantonsspital, Baar, Switzerland.

Declaration of competing interest

None.

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