
Article:
Rowbotham, EL, Freeston, JE, Emery, P et al. (1 more author) (2015) The prevalence of tenosynovitis of the interosseous tendons of the hand in patients with rheumatoid arthritis. European Radiology. ISSN 0938-7994

https://doi.org/10.1007/s00330-015-3859-0

Title Page (Title, Authors, Institutions, Contact Information)

The prevalence of peri-tendinous inflammation of the interosseous tendons of the hand in patients with rheumatoid arthritis

Emma L Rowbotham FRCR

Musculoskeletal Radiology Department, Leeds Teahcing Hospitals NHS Trust

Jane E Freeston FRCP

Consultant Rheumatologist and Honorary Senior Lecturer, Leeds Teaching Hospitals NHS Trust

Paul Emery MA MD FRCP

Arthritis Research UK Professor of Rheumatology Leeds Musculoskeletal Biomedical Research Unit, LTHT Leeds Institute of Rheumatic Musculoskeletal Medicine University of Leeds

Andrew J Grainger FRCR

Department of Musculoskeletal Radiology, Leeds Teaching Hospitals Trust, Leeds NIHR Leeds Musculoskeletal Biomedical Research Unit, Chapel Allerton Hospital, Leeds

This is an original research paper

Leeds Biomedical Medical Research Unit Chapel Allerton Hospital Leeds Teaching Hospitals Trust Leeds

LS7 4SA

(0113) 392 4474 Corresponding author – emmarowbotham@nhs.net

The prevalence of tenosynovitis of the interosseous tendons of the hand in patients with Rheumatoid Arthritis

Abstract:

Aim: The aim of this study was to establish the prevalence of tenosynovitis affecting the interosseous tendons of the hand in a rheumatoid arthritis (RA) population; also to assess for association with metacarpophalangeal (MCP) joint synovitis, flexor tendon tenosynovitis or ulnar drift.

Methods: 44 patients with RA underwent MRI of the hand along with 20 normal controls. Coronal 3D T1 VIBE sequences pre and post contrast were performed and reconstructed. The presence of interosseous tendon tenosynovitis was recorded alongside MCP joint synovitis, flexor tendon tenosynovitis and ulnar drift.

Results: 21 (47.7%) patients with RA showed interosseous tendon tenosynovitis. 52 (14.8%) interosseous tendons showed tenosynovitis amongst the RA patients. Interosseous tendon tenosynovitis was more commonly seen in association with adjacent MCP joint synovitis ($p<0.001$), but 9 MCP joints (5.1%) showed adjacent interosseous tenosynovitis in the absence of joint synovitis. Interosseous tendon tenosynovitis was more frequently seen in fingers which also showed flexor tendon tenosynovitis ($p<0.001$) and in patients with ulnar drift of the fingers ($p=0.01$).

Conclusion

Tenosynovitis of the hand interosseous tendons was found in 47.7% of patients with RA. In the majority of cases this was adjacent to MCP joint synovitis; however, interosseous tendon tenosynovitis was also seen in isolation.

Key Points:

1. Tenosynovitis of the interosseous tendons of the hand occurs in rheumatoid arthritis
2. Interosseous tendon tenosynovitis has a prevalence of 47.7% in patients with RA
3. Interosseous tendon tenosynovitis is related to MCP joint synovitis in the adjacent joints

Keywords: Rheumatoid Arthritis; interosseous tendons;Magnetic Resonance Imaging

Inflammation; synovitis

The prevalence of tenosynovitis of the interosseous tendons of the hand in patients with Rheumatoid Arthritis

Introduction:

Synovitis of the joints of the hands is the characteristic abnormality in patients with rheumatoid arthritis (RA) [1]. Tendon disease, including tenosynovitis, tendinopathy and tendon rupture are also well-recognized findings in this condition occurring frequently in both the hands and the wrist. Tenosynovitis of both the flexor and extensor tendons is common and well documented with a reported incidence in RA patients of approximately 48% [2, 3]. Indeed it has recently been reported to be the first sign of pathology in the pre-clinical phase of RA [3, 4]. Tendinopathy is linked to an increased risk of tendon rupture which in turn can contribute to deformity and abnormal angulation at the small joints. Imaging is usually employed in cases of inflammatory arthropathy, being objective and more sensitive than clinical examination [5-7]. Conventional radiographs, ultrasound and MRI may all be used both for diagnostic purposes, and as a means of assessing disease progression and response to treatment. Ultrasound and MRI are both able to demonstrate associated tenosynovitis in the flexor and extensor tendons, although the sensitivity of MRI for this form of the disease has been shown to be higher [2].

The interosseous muscles of the hand arise from the metacarpal shafts and insert variably onto the proximal phalanx of each finger, the extensor hood and the volar plate through a short tendon [8] (Figure 1). There are four dorsal and three palmar interosseous muscles which act through their respective tendons across the metacarpo-phalangeal (MCP) joints; their principal action is to abduct

(dorsal interossei) and adduct (palmar interossei) the digits. Each finger is provided with two interosseous muscles. Abduction and adduction of the fingers is described relative to the middle finger, which therefore only abducts and is consequently served by two dorsal interosseous muscles. The index and ring fingers each have a dorsal and a palmar interosseous muscle. The little finger has a palmar interosseous muscle, but the place of the dorsal interosseous muscle is taken by the abductor digiti minimi (ADM) muscle also acting through a short tendon. Tenosynovitis associated with these interosseous tendons has not, to our knowledge, been previously documented.

The aim of this study was to report the presence of interosseous tendon tenosynovitis, a feature we have observed in patients with RA, and establish its prevalence. Given the close relationship of the interosseous tendons to the joints we also looked to see if inflammation involving the interosseous tendons existed independently of joint synovitis. Finally, since the interosseous tendons are responsible for abduction and adduction at the MCP joints and ulnar drift is a recognised feature of RA [9, 10], we examined whether there was an association between ulnar drift and tenosynovitis involving the interosseous tendons. Given the action of ADM is to abduct the little finger, this was also assessed and the term interosseous tendons is used to include the tendons of the dorsal and palmer interosseous muscles, along with the tendon of ADM throughout this paper.

Methods:

Patient population:

The study population comprised 44 patients with inflammatory arthritis fulfilling ACR/EULAR 2010 classification criteria [11] for RA and 20 control subjects. The control subjects were negative for rheumatoid factor and anti-citrullinated protein antibodies and had no history, symptoms or clinical evidence of inflammatory arthritis. All subjects had consented to inclusion and approval had been given by the local ethics committee. Two groups of patients were included. A group of newly diagnosed patients comprising 16 patients enrolled at the time of initial disease presentation and diagnosis who had not received disease modifying therapy. These patients had mean symptom duration of 15.4 months (3 to 33 months) before presentation. The remaining 28 patients comprised those with an established diagnosis of RA for at least 1 year, these patients had a mean disease duration from diagnosis of 11.2 years (range 1 to 24 years).

MRI scanning:

All patients and controls underwent MRI of the hand and wrist, selecting the most symptomatic side for imaging. MRI was undertaken on either a 1.5T Siemens Avanto or 3T Siemens Verio system (Siemens, Erlangen Germany), using a protocol which included pre and post contrast coronal 3D T1 spoiled gradient echo (VIBE) sequences, with isotropic voxels allowing subsequent reconstruction in three planes. The parameters for the VIBE sequences at 1.5T were Repetition Time (TR)=30ms, Echo Time (TE)=6.82ms and Flip Angle (FA)=30 degrees. For the 3T sequences these parameters were TR=12ms,

TE=3.06ms and FA=30 degrees. On both systems the voxel size was 0.5mm^3. An 8 channel knee coil was used.

Image analysis:

Two experienced fellowship trained MSK radiologists independently reviewed the MRI studies of all the subjects. The studies were presented in random order and the observers were blind to disease status (control, newly diagnosed or established RA). The presence or absence of tenosynovitis associated with the interosseous tendons was recorded. This was defined as the presence of enhancing tissue surrounding the tendon and evident in at least two planes. 8 tendons were evaluated in each hand, those of the dorsal interossei (1 to 4), the palmar interossei (1 to 3) and the abductor digiti minimi. The observers were careful to distinguish inflammatory change relating to the interosseous tendon from synovitis in the adjacent MCP joints. However the presence or absence of joint synovitis in the MCP joints adjacent to the interosseous tendons (index, middle, ring and little MCP joints) was also recorded. Any discrepancies between the observers were reviewed and agreed by consensus.

Tenosynovitis affecting the flexor tendons to the index, middle, ring and little fingers was also recorded. This was identified as the presence of peritendinous effusion and/or synovial proliferation with enhancement, and in keeping with other published work was only recorded if visible over a length of 6 mm [12](Figure 2). For the purposes of the study the flexor tendons were evaluated distal to the carpometacarpal joints.

Angulation at the third MCP joint was measured on PA radiographs for each case. An angle of greater than 10 degrees was recorded as ulnar drift in keeping with

definitions from previous work [13]. The Chi Squared test was used for statistical analysis, and the kappa statistic was used to assess interobserver agreement.

Results:

The demographics for the control subjects and two patient groups (newly diagnosed and established RA) are given in table 1.

Agreement between observers:

The two observers showed an excellent level of agreement for the identification of interosseous tendon tenosynovitis: kappa (k) = 0.91, (Standard Error (SE) = 0.03). High levels of agreement were also seen for the assessment of metacarpal phalangeal joint synovitis (k=0.84, SE=0.03) and flexor tendon tenosynovitis (k=0.84, SE-0.04).

Interosseous tendon tenosynovitis:

Amongst the control group no tenosynovitis was identified involving the tendons of the interosseous muscles.

21 of 44 (47.7%) patients showed tenosynovitis in one or more interosseous tendons and/or in the ADM (Figure 3, 4 5). The majority of these patients showed involvement of only 1 (7 patients) or 2 (8 patients) tendons, although 3 patients showed tenosynovitis in 4 tendons, 2 showed it in 5 tendons and 1 patient had involvement of 7 of the 8 tendons.

8 interosseous tendons in each hand meant that amongst the 44 patients there were a total of 352 tendons. In the patient group 52 of 352 interosseous tendons showed tenosynovitis (14.8%) (Table 2). The most commonly involved tendon was that of the first dorsal interosseous. As can be seen from table 2 the

tenosynovitis was more prevalent in the patients with established RA (40/224 17.9%) compared to those with newly diagnosed disease (12/128 9.4%). No cases of tendon rupture were identified

MCP joint synovitis:

Synovitis was seen in 96 (54.4%) of the 176 MCP joints in the patient group (39 of 44 patients). In the control group 7 MCP joints (8.8%) showed synovitis (4 subjects) (Table 3). Each finger MCP joint is associated with two of the interosseous muscle tendons evaluated (Figure 1); these pass adjacent to the joint capsule. In 35 (19.9%) MCP joints synovitis was seen along with interosseous tenosynovitis in one or both of the adjacent interosseous tendons. In 9 (5.1%) MCP joints (5 patients) one or both of the adjacent interosseous tendons showed tenosynovitis with no evidence of inflammation in the MCP joint itself. Interosseous tendon tenosynovitis was more frequently seen adjacent to MCP joints with synovitis than those without ($p<0.001$).

Flexor Tendon tenosynovitis:

Amongst the patient group 74 of 176 (42.0%) flexor tendons showed tenosynovitis (29 of 44 patients). One control subject showed flexor tenosynovitis in a single tendon (Table 4). 26 (14.8%) fingers in the patient group showed both flexor tenosynovitis and tenosynovitis in one or both of the interosseous tendons. Interosseous tendon tenosynovitis without flexor tendon tenosynovitis was seen in 18 (10.2%) fingers. Tenosynovitis in the interosseous tendons was more frequently seen in fingers also showing flexor tenosynovitis compared to those without ($p<0.001$).

Ulnar drift:

12 patients showed evidence of ulnar drift. Interosseous tendon tenosynovitis was more commonly seen amongst patients with ulnar drift (9/12, 75%), compared to patients with normal MCP joint alignment (10/32, 31%), p=0.01. Ulnar drift was not seen amongst the control subjects.

Discussion:

The interosseous muscles of the hand have been described as the "foundation of hand function" having an important role in finger balance, grip and pinch function[14]. The complex distal insertions of the tendons from these muscles into the extensor expansion of the fingers as well as into bone, have been the subject of extensive study and it is clear that the view of the interosseous muscles as merely acting to abduct and adduct the fingers is simplistic, with the muscles also acting to assist with flexion at the MCP joints and extension of the interphalangeal joints, balancing the actions of other muscles on the fingers [15]. There is little pathology related to these tendons and muscles documented in the literature, dysfunction usually being the result of nerve palsy, ischaemic contracture and fractures [15]. Overuse tendinitis of the interosseous muscles of the hands, although relatively rare, is a recognised phenomenon and occurs as a result of overuse usually related to occupation, for instance it is well described in pianists. However, our study suggests that there is a high prevalence of inflammation about the interosseous tendons in patients with RA, a phenomenon that has not previously been recognized.

For the purposes of this study we have described the inflammatory change associated with the tendons of the interosseous muscles and ADM as tenosynovitis. However we recognise that the microstructure of these tendons has not been well described despite the fact that several papers exist describing the complex, and often very variable, tendon insertions [16]. It is therefore unclear whether these tendons have a true tenosynovium or whether the observation would be better described as paratenonitis, a term used for inflammation around tendons without tendon sheaths such as the Achilles tendon. Frequently tenosynovitis is also associated with fluid in the tendon sheath and this was not a feature identified in association with any of the interosseous tendons. However, further studies are needed to confirm the presence or absence of a tenosynovium associated with these tendons before we can be more specific as to the nature of the inflammation observed. The changes we observed were of post-gadolinium contrast enhancement of the tissue surrounding the tendons, similar to the well recognised appearance of enhancing joint and tenosynovium. Further studies will determine whether these abnormalities can be seen without the use of contrast medium; although a recent report has highlighted the continued need for gadolinium contrast for the sensitive and specific detection of synovitis and tenosynovitis in patients with inflammatory arthritis [17].

We did not specifically interrogate either the myotendinous junction or the enthesis and this may form the basis of further work in this area, particularly in patients with seronegative arthritis. We acknowledge other limitations of this study, which had the primary aim of identifying and describing an apparently new finding in patients with RA. It was not possible to image all study subjects

on the same scanner due to constraints within our department. Protocols were optimised to produce images of the same resolution on each system. It should also be noted that both systems identified patients with interosseous tenosynovitis.

A knee coil was used to image the hands in this study in accordance with our departmental protocol for imaging the hand and wrist in rheumatoid arthritis. This coil provides coverage of all the interphalangeal joints and the wrist joint in a single field of view. However we recognise that higher resolution imaging of the small interosseous tendons may be achieved with an optimised coil such as a wrist coil. The potential for high resolution imaging with a surface coil in arthritis of the hand has been demonstrated and represents a potential area for further work to investigate the interosseous tendons in these conditions [18].

It is likely that tenosynovitis associated with the interosseous tendons may be a cause of symptoms and therefore should be documented and potentially treated with the same clinical importance as both joint synovitis and tenosynovitis elsewhere in patients with inflammatory arthritis. Further studies in this area with clinical correlation to symptoms are needed to determine whether this phenomenon is symptomatic or not. It remains to be identified whether or not the inflammatory change we report predisposes the affected tendon to dysfunction or rupture. If this proved to be the case it may be a predisposing factor for the development of hand deformities in patients with RA. None of the cases in our study showed evidence of tendon rupture.

In the majority of cases synovitis was seen at the MCP joint adjacent to the interosseous tendons displaying tenosynovitis. This is in keeping with previous studies showing that, in patients with RA, pathology involving both the joints and

the tendons often coexists, particularly in advanced disease. Previous studies have found that flexor and extensor tenosynovial inflammation is frequently found adjacent to areas of synovitis at the wrist and it has been suggested that inflammatory change within the tenosynovium mirrors that of the synovial membrane, particularly in early disease [19]. We also found interosseous tendon tenosynovitis was more likely to be seen in digits where there was also flexor tendon tenosynovitis, than in those without. It is unclear from our data whether inflammatory change associated with the interosseous tendons is a primary or secondary phenomenon. However, it is important to recognize that we identified 9 cases of interosseous peri-tendinous inflammation without inflammation in the adjacent MCP joint. This may be one explanation for the presence of MCP joint symptoms in the absence of active joint synovitis using clinical or imaging criteria. This is of particular relevance given the recent finding that flexor tenosynovitis may be the first pathology in RA [3] [4].

We have also demonstrated that interosseous tendon tenosynovitis is more frequently seen in patients with ulnar drift at the MCP joints. This may simply reflect the increased severity of the disease in these patients or may be a consequence of the increased mechanical stress consequent of ulnar drift.

In conclusion, we have identified the presence of enhancing tissue around the tendons of the interosseous muscles in the hands of patients with both newly diagnosed and established RA. This is felt to be inflammatory in nature, in keeping with well-documented similar changes associated with other tendons in patients with RA. While the significance of this observation remains to be established it does have implications for those undertaking imaging of RA, both as a potential further site for the detection of inflammation and as a pitfall if it is

confused with MCP joint synovitis. Given the close relationship of these tendons to the MCP joints, inflammation associated with the interosseous tendons may also be a cause of joint symptomatology in the absence of clinical or imaging evidence of joint inflammation. Further studies will elucidate whether there is a correlation with early morning stiffness of the hands, a characteristic feature of RA, which correlates poorly with synovitis [20].

Summary Statement: Tenosynovitis of the interosseous tendons of the hand is a newly described phenomenon in patients with RA. This is an important new finding which may potentially be symptomatic in patients previously thought to have painful MCP joint synovitis.

Figures:

Figure 1a Anatomy - Illustration of the anatomy of the dorsal interosseous tendons of the hand. This illustration demonstrates the origin of the interossei from the medial and lateral aspects of the metacarpals. The attachments into the extensor hood and proximal phalanx of each finger is also demonstrated. The little finger is abducted by the abductor digiti minimi (not shown).

Figure 1b Anatomy – Illustration of the anatomy of the palmar interosseous tendons. There are three palmar interossei which attach to the index, ring and little fingers. They are smaller than the dorsal interossei of the hand.

Figure 1c: Anatomy – axial MR image through the hand to illustrate the anatomy of the palmar (yellow arrows) and dorsal (red arrows) interosseous tendons on cross sectional imaging. The abductor digiti minimi is also shown (white arrow)

Figure 2 – Interosseous tendon tenosynovitis was defined as high signal change around the tendon on post contrast images (blue circle)

Figure 3 – Coronal reformat of the first dorsal interosseous tendon showing tenosynovitis. There is no adjacent MCP joint synovitis seen in this case.

Figure 4 - Axial post contrast image showing tenosynovitis of the fourth dorsal interosseous tendon (blue circle). A prominent erosion within the radial aspect of the ring finger metacarpal head (asterix) is seen in this patient with established RA. This patient also had MCP joint synovitis in all of the MCP joints (only fourth MCP joint synovitis seen on this figure - arrows)

Figure 5 - Axial post contrast image showing florid tenosynovitis of the index and ring finger flexor tendons and interosseous peri tendinous inflammation affecting the third palmar interosseous tendon (blue circle).

References:

1. Brook, A. and M. Corbett, *Radiographic changes in early rheumatoid disease.* Ann Rheum Dis, 1977. **36**(1): p. 71-3.
2. Wakefield, R.J., et al., *Finger tendon disease in untreated early rheumatoid arthritis: a comparison of ultrasound and magnetic resonance imaging.* Arthritis Rheum, 2007. **57**(7): p. 1158-64.

3. Navalho, M., et al., *Bilateral MR imaging of the hand and wrist in early and very early inflammatory arthritis: tenosynovitis is associated with progression to rheumatoid arthritis.* Radiology, 2012. **264**(3): p. 823-33.
4. Rakieh, C., et al., *OP0180 Rsk of Developing Clinical Synovitis in ACPA Positive Patients with Non-specific Musculoskeletal Symptoms. .* Annals of the Rheumatic Diseases 2013. **72**(Supple 3): p. A114.
5. Wakefield, R.J., et al., *The value of sonography in the detection of bone erosions in patients with rheumatoid arthritis: a comparison with conventional radiography.* Arthritis Rheum, 2000. **43**(12): p. 2762-70.
6. Brown, A.K., et al., *New approaches to imaging early inflammatory arthritis.* Clin Exp Rheumatol, 2004. **22**(5 Suppl 35): p. S18-25.
7. Goupille, P., et al., *Magnetic resonance imaging: a valuable method for the detection of synovial inflammation in rheumatoid arthritis.* J Rheumatol, 2001. **28**(1): p. 35-40.
8. Eladoumikdachi, F., et al., *Anatomy of the intrinsic hand muscles revisited: part I. Interossei.* Plast Reconstr Surg, 2002. **110**(5): p. 1211-24.
9. Hastings, D.E. and J.A. Evans, *Rheumatoid wrist deformities and their relation to ulnar drift.* J Bone Joint Surg Am, 1975. **57**(7): p. 930-4.
10. Johnsson, P.M. and K. Eberhardt, *Hand deformities are important signs of disease severity in patients with early rheumatoid arthritis.* Rheumatology (Oxford), 2009. **48**(11): p. 1398-401.
11. Aletaha, D., et al., *2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative.* Ann Rheum Dis, 2010. **69**(9): p. 1580-8.
12. Haavardsholm, E.A., et al., *Introduction of a novel magnetic resonance imaging tenosynovitis score for rheumatoid arthritis: reliability in a multireader longitudinal study.* Ann Rheum Dis, 2007. **66**(9): p. 1216-20.
13. DiBenedetto, M.R., L.M. Lubbers, and C.R. Coleman, *Relationship between radial inclination angle and ulnar deviation of the fingers.* J Hand Surg Am, 1991. **16**(1): p. 36-9.
14. Kozin, S.H., *Arthroplasty of the hand and wrist: surgeon's perspective.* J Hand Ther, 1999. **12**(2): p. 123-32.
15. Liss, F.E., *The interosseous muscles: the foundation of hand function.* Hand Clin, 2012. **28**(1): p. 9-12.
16. Ikebuchi, Y., T. Murakami, and A. Ohtsuka, *The interosseous and lumbrical muscles in the human hand, with special reference to the insertions of the interosseous muscles.* Acta Med Okayama, 1988. **42**(6): p. 327-34.
17. Stomp, W., et al., *Aiming for a simpler early arthritis MRI protocol: can Gd contrast administration be eliminated?* Eur Radiol, 2015. **25**(5): p. 1520-7.
18. Tan, A.L., et al., *High-resolution magnetic resonance imaging for the assessment of hand osteoarthritis.* Arthritis Rheum, 2005. **52**(8): p. 2355-65.
19. Jain, A., et al., *Production of cytokines, vascular endothelial growth factor, matrix metalloproteinases, and tissue inhibitor of metalloproteinases 1 by tenosynovium demonstrates its potential for tendon destruction in rheumatoid arthritis.* Arthritis Rheum, 2001. **44**(8): p. 1754-60.
20. Yazici, Y., et al., *Morning stiffness in patients with early rheumatoid arthritis is associated more strongly with functional disability than with*

joint swelling and erythrocyte sedimentation rate. J Rheumatol, 2004. **31**(9): p. 1723-6.

Table 1
Click here to download Table: Table 1.docx

Table 1: Demographics of the control subjects and patients

	n	Sex (Male/Female)	Mean Age (range)
Control Subjects	20	5/15	49 (25-64)
Newly Diagnosed RA	16	6/10	51 (24-73)
Established RA	28	2/26	51 (29-76)

Table 2
Click here to download Table: Table 2.docx

Table 2: Intrinsic tendons showing peritendinous inflammation (number of tendons)

	n	Dorsal Interossei				Palmar Interossei			ADM	TOTAL (%)
		1	2	3	4	1	2	3		
Newly Diagnosed RA	128	4	1	0	1	0	1	1	4	12 (9.4)
Established RA	224	9	6	1	6	3	4	8	3	40 (17.9)
Total	352	13	7	1	7	3	5	9	7	52 (14.8)

Table 3
Click here to download Table: Table 3.docx

Table 3: Distribution of MCP joint synovitis (number of joints)

	n	Index	Middle	Ring	Little	Total (%)
Controls (20 subjects)	80	2	0	1	4	7 (8.8)
Patients (44 subjects)	176	27	25	21	23	96 (54.4)

Table 4
Click here to download Table: Table 4.docx

Table 4: Distribution of Flexor Tendon tenosynovitis

	n	Index	Middle	Ring	Little	Total (%)
Controls (20 subjects)	80	1	0	0	0	1 (1.3)
Patients (44 subjects)	176	22	17	17	18	74 (42.0)

Figure 1a
Click here to download Figure: Figure 1a.tiff

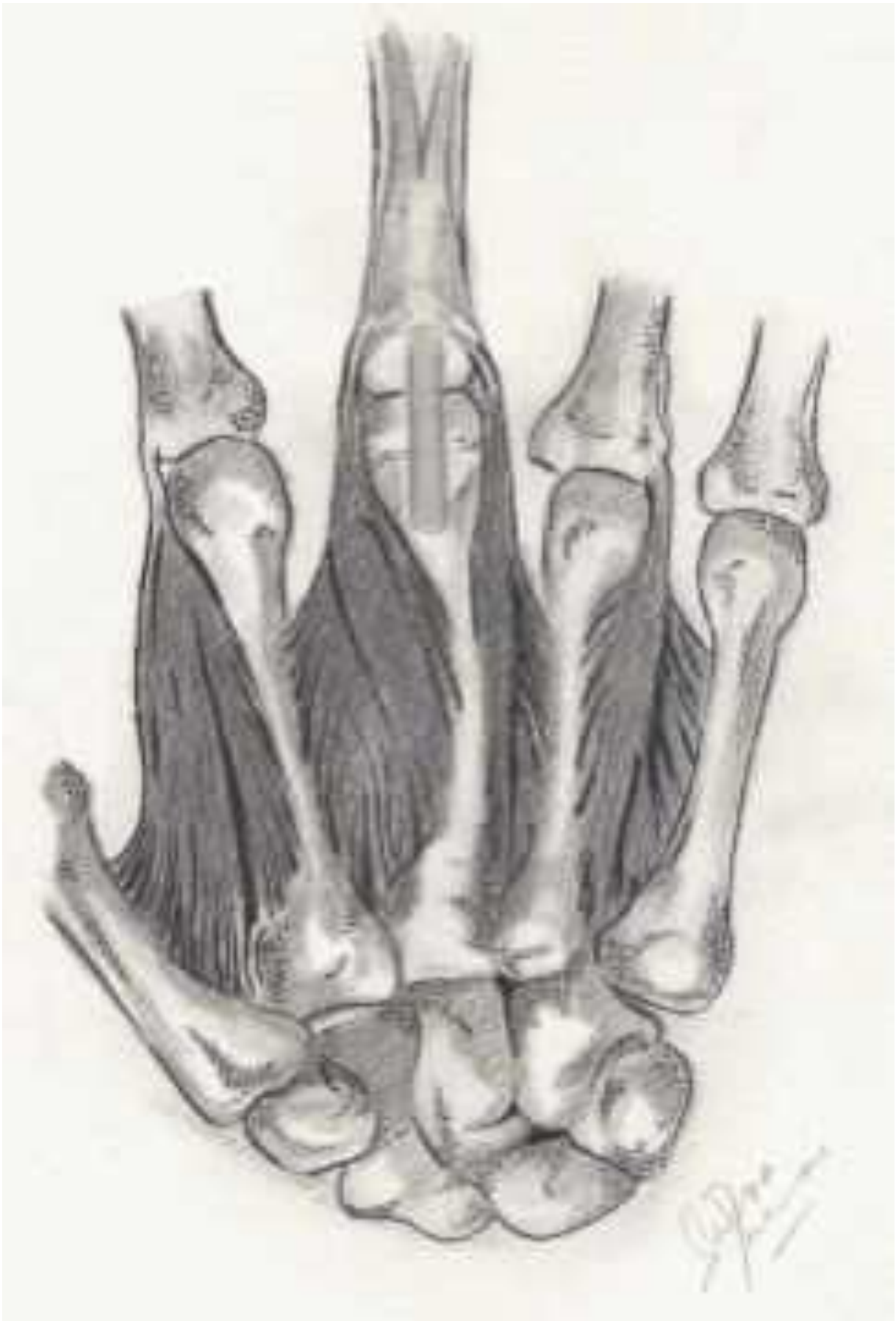


Figure 1b
Click here to download Figure: Figure 1b.tiff

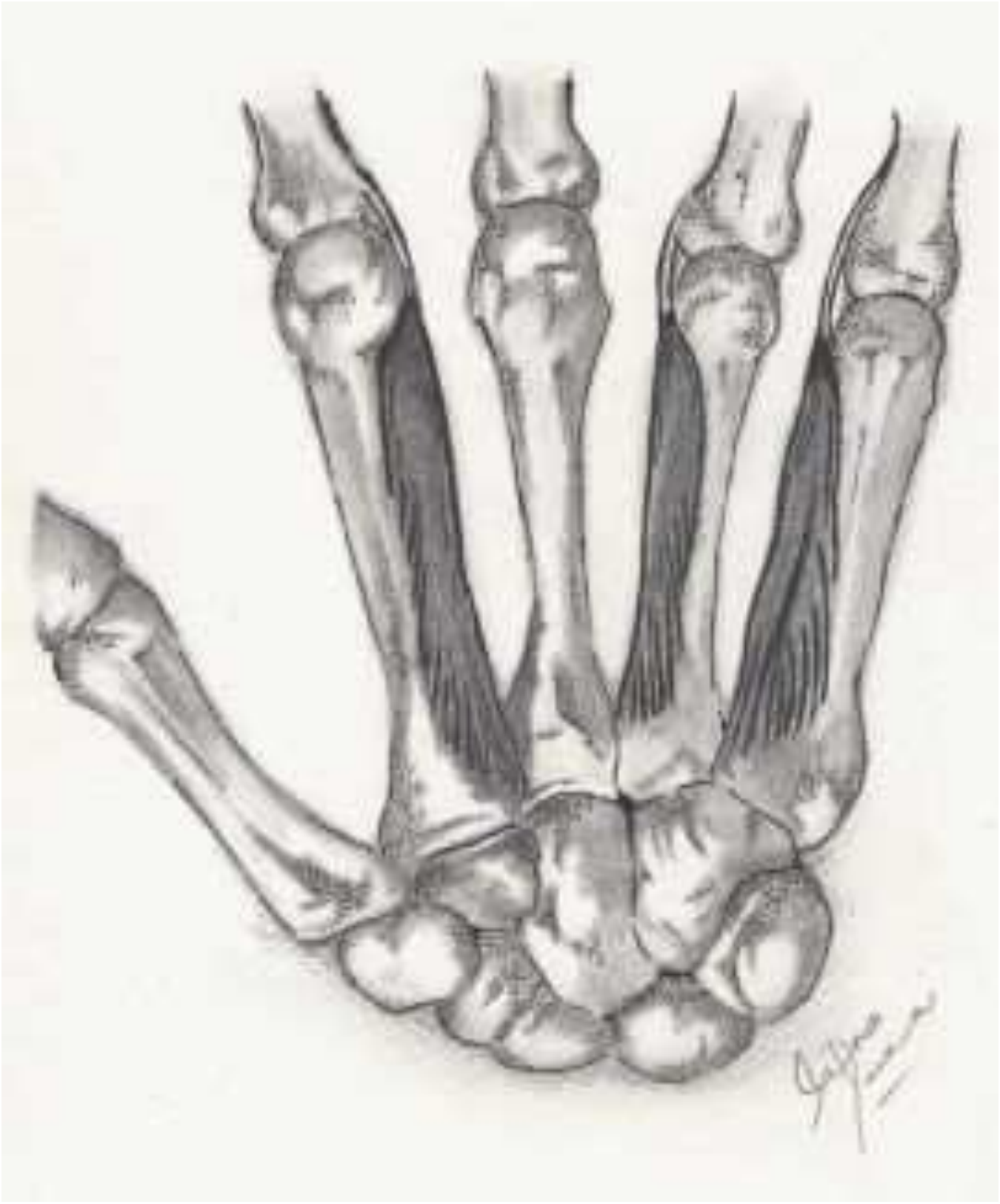


Figure 1c
Click here to download Figure: Figure 1c.tiff

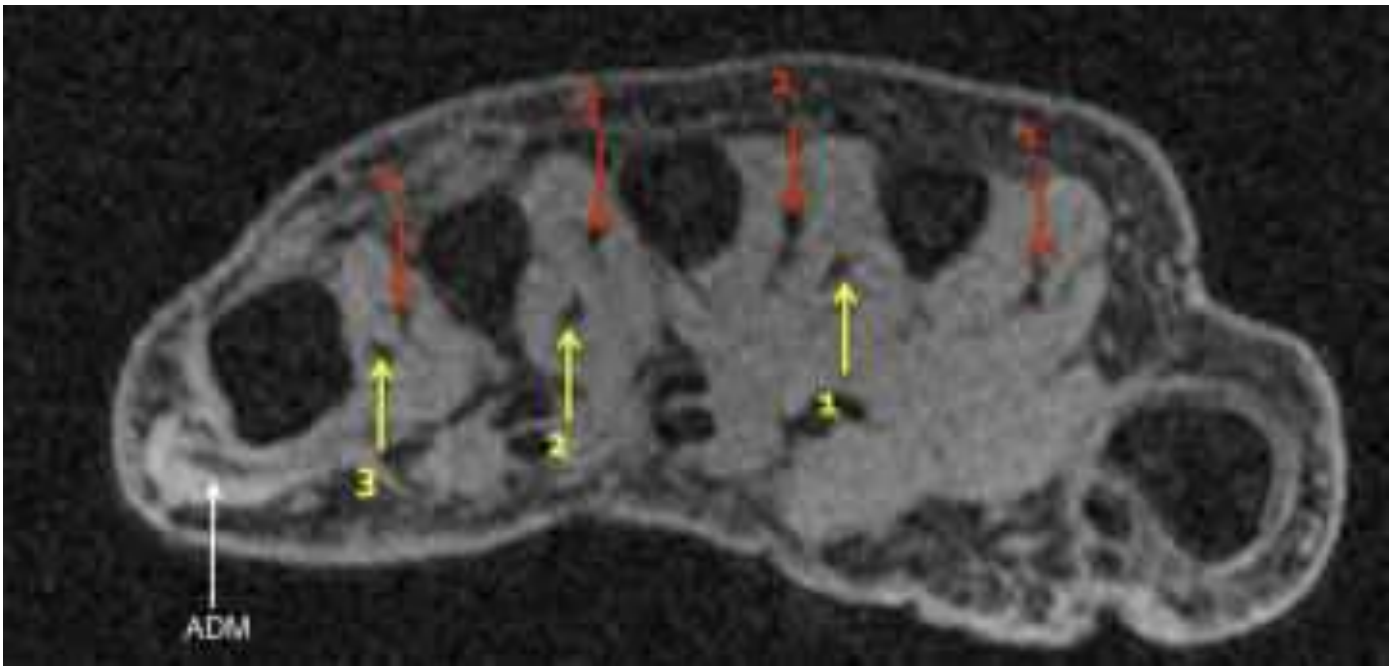


Figure 2
Click here to download Figure: Figure 2.tiff

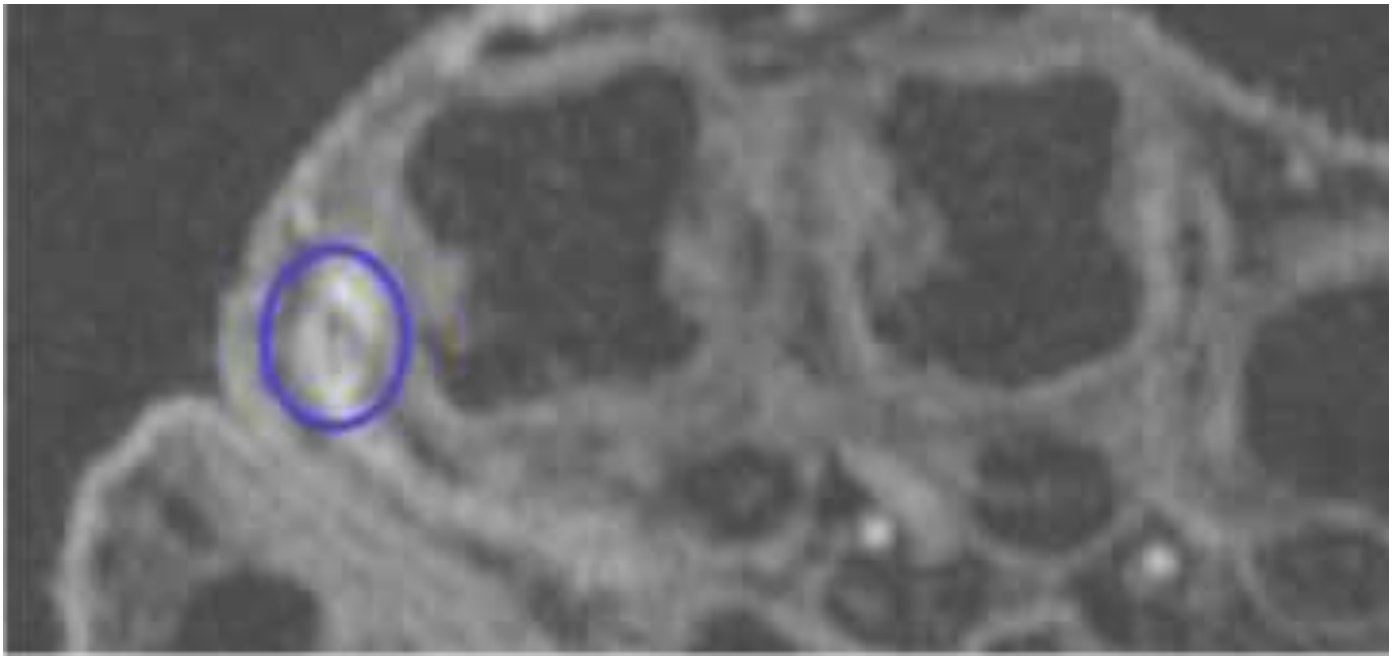


Figure 3
Click here to download Figure: Figure 3.tiff

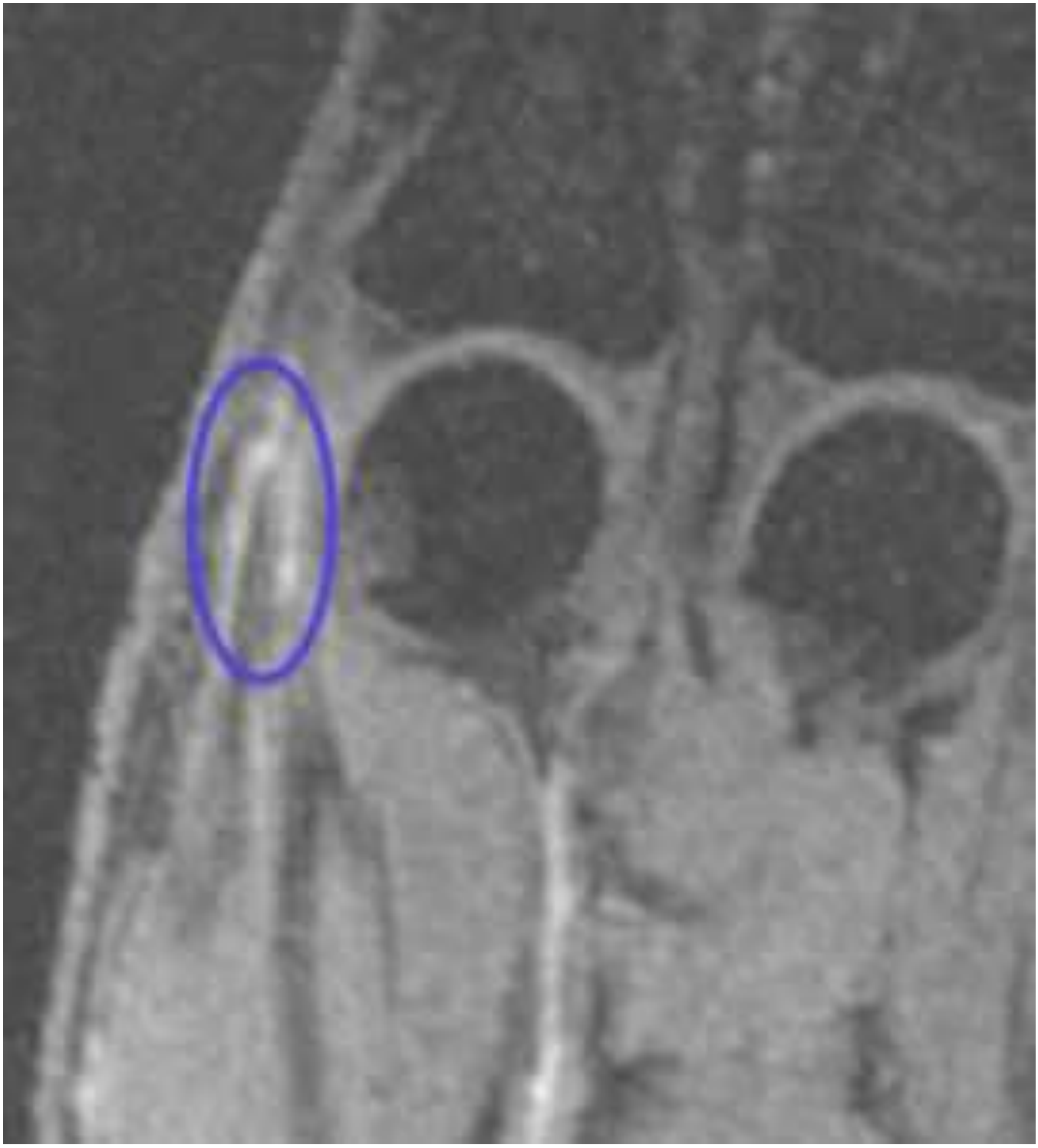


Figure 5
Click here to download Figure: Figure 5.tiff

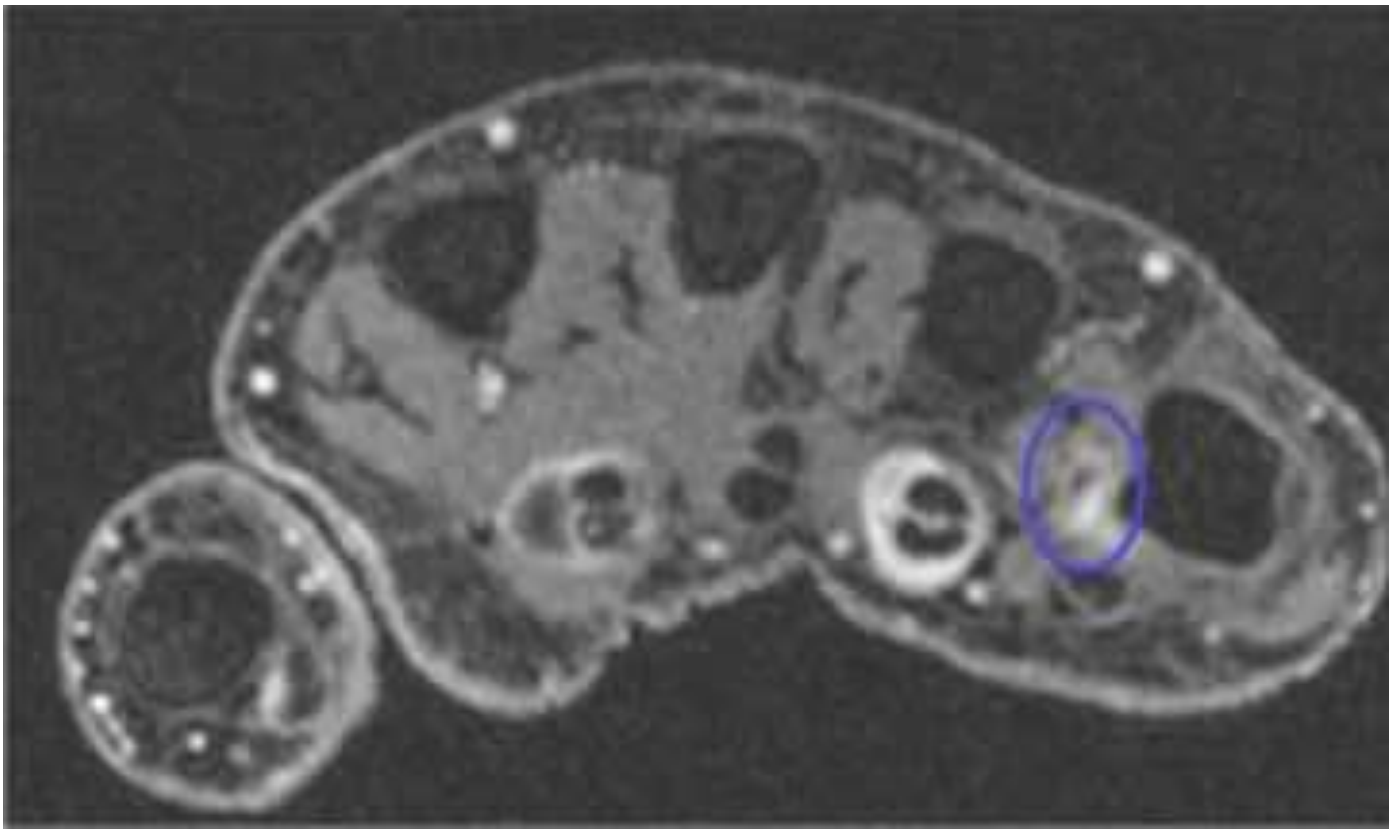
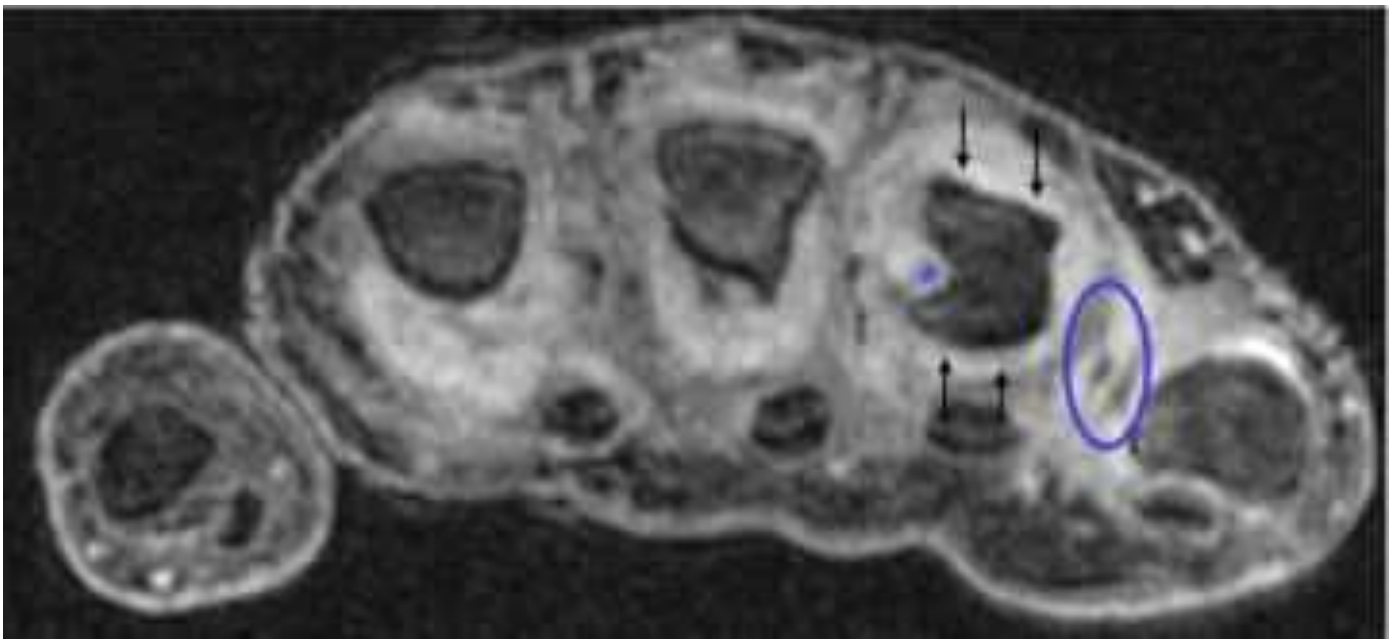


Figure 4
Click here to download Figure: Figure 4.tiff



Disclosure Paragraph
Click here to download Disclosure Paragraph: Disclosure Paragraph-2.doc

Please fill in the appropriate responses as indicated in the menu point *Additional Information*, and delete the sentences that are not applicable for your manuscript. Upload the completed Disclosure document together with your manuscript files, with the file designation „Disclosure Paragraph".
The paragraph will be published in the acknowledgements section of your paper.

Disclosure paragraph:

1) The scientific guarantor of this publication is Dr Andrew Grainger

2) The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

3) The authors state that this work has not received any funding.

4) No complex statistical methods were necessary for this paper.

5) Institutional Review Board approval was obtained.

6) *Only if the study is on human subjects:*
Written informed consent was obtained from all subjects (patients) in this study.

7) *Only if the study is on animals: N/A*

8) N/A

9) Methodology:
- prospective
- observational
- performed at one institution