

# MRI Features in Transthyretin Amyloidosis of the Carpal Tunnel and Amyloid-Negative Control: A Case Report

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## Case Report

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# Abstract

Amyloidosis is a systemic disorder characterized by extracellular protein deposition, with transthyretin amyloidosis being the most common subtype. Carpal tunnel syndrome is a frequent early manifestation, yet detailed MRI characterization of amyloid deposition in the wrist remains limited.

We present MRI findings from one severe transthyretin amyloidosis case: a 65-year-old male with severe carpal tunnel syndrome secondary to transthyretin amyloidosis wild-type. The subject underwent wrist MRI using T1 and proton density sequences. This case demonstrated extensive flexor tendon thickening, severe tenosynovitis, and hyperintense, striated amyloid deposition within the tenosynovium.

MRI revealed distinct patterns of amyloid involvement in carpal tunnel syndrome, highlighting potential imaging biomarkers for characterizing transthyretin amyloidosis and enabling the early detection of cardiac involvement. These findings highlight the potential of MRIs in non-invasive amyloid characterization. As such, larger studies would be required to further validate these observations and integrate MRI into early amyloidosis diagnostic pathways.

## Introduction

Amyloidosis is a systemic disorder characterized by extracellular deposition of misfolded proteins as insoluble fibrils in various tissues [1, 2]. Among its subtypes, transthyretin amyloidosis (ATTR) is a particular case stemming from the misfolding of transthyretin, a transport protein primarily synthesized in the liver, with a prevalence of 16.6 cases per million people [3]. These insoluble amyloid fibrils progressively infiltrate organ systems and connective tissues, leading to structural disruption and loss of function. Two major subtypes are recognized: hereditary ATTR, which stems from mutations in the TTR gene, and wild-type ATTR (ATTRwt), which is associated with aging [1, 4]. Furthermore, ATTRwt is increasingly recognized as a common cause of heart failure in older adults [1], but early extra-cardiac manifestations, particularly within the musculoskeletal system, are frequently underappreciated [6–7].

Carpal tunnel syndrome (CTS) is one of the earliest and most prevalent peripheral manifestations of ATTR amyloidosis, with studies estimating that approximately 10–15% of patients with CTS have underlying amyloid deposition [6]. CTS arises from compression of the median nerve within the carpal tunnel and typically presents with pain, numbness, and hand weakness. In the setting of ATTR, amyloid deposits accumulate in the flexor tendons, transverse carpal ligament, and surrounding tenosynovium, leading to tissue hypertrophy and progressive nerve entrapment (Fig. 1) [7].

Indeed, CTS often precedes the diagnosis of systemic ATTR by 4 to 10 years and may serve as an indicator for both ATTRwt and ATTRv [7–9]. Recognition of this relationship is critical, as bilateral CTS in older patients may reflect underlying systemic amyloidosis.

While histopathological confirmation through biopsy remains the diagnostic reference standard, it is only performed in patients with severe carpal tunnel syndrome and willing to undergo release surgery.

Imaging may play an important role in the non-invasive assessment of amyloid-related CTS. Conventional MRI can detect morphological abnormalities such as tendon thickening and nerve enlargement but lacks specificity for amyloid infiltration. These MRI findings may allow clinicians to identify patients who warrant further diagnostic evaluation using histopathological testing, facilitating diagnosis before cardiac or other organ involvement becomes clinically apparent.

In this report, we describe the MRI findings in a 65-year-old male with biopsy-confirmed wild-type ATTR and bilateral CTS. This case shows distinct imaging features of amyloid involvement in the carpal tunnel, including striated hyperintensity within the thickened tenosynovium and flexor tendons. Few studies to date have detailed amyloid-associated alterations in the wrist. As such, this case highlights the diagnostic potential of MRI in identifying early peripheral amyloid involvement and may guide future research aimed at integrating musculoskeletal imaging into the diagnostic pathway for systemic amyloidosis.

## Case Report

A 65-year-old male first presented to the clinic for cardiac evaluation. His past medical history included a remote episode of pericarditis in 2009, without clinical signs of congestive heart failure. Subsequent investigations led to a diagnosis of ATTRwt. At the time of cardiac evaluation, the patient reported persistent mild numbness in the right wrist. He had a history of severe bilateral CTS, more pronounced on the right, characterized by chronic numbness, pain, and sharp tingling sensations. He had previously undergone bilateral carpal tunnel release surgery and histopathological analysis of tenosynovial tissue obtained during the procedure revealed amyloid deposition, which retrospectively confirmed the diagnosis of ATTRwt in 2022. No pre-operative MRI of the wrists was performed prior to the carpal tunnel release procedures.

Wrist MRI was performed on April 12, 2024, to further investigate persistent CTS-related symptoms. At the time of evaluation, no pharmacological treatment targeting ATTRwt had been initiated. The protocol included T1-weighted and proton density sequences. Following MRI comparison with a 76 year old amyloid negative patient with moderate-severe CTS, imaging revealed multiple findings consistent with amyloid deposition. There was marked thickening of the flexor tendons bilaterally, with abnormal signal intensity qualified as striated and heterogeneous infiltration. The tenosynovium appeared hyperintense with internal striations and diffuse thickening. The carpal tunnel itself exhibited a cloudy appearance suggestive of fluid accumulation, potentially representing edema. The median nerve was severely compressed, with visible enlargement, nodular thickening, and disrupted fascicular architecture. Moderate-to-severe thickening of the flexor retinaculum was also observed (Fig. 2).

Further quantitative analysis demonstrated that the ATTR subject exhibited overall larger tissue structures compared with the amyloid-negative subject (Table 1).

| Quantitative Features      | ATTRwt                                    | Amyloid Negative                          |
|----------------------------|-------------------------------------------|-------------------------------------------|
| CSA of Carpal Tunnel       | Right: 2.81   Left: 2.62<br>Average: 2.72 | Right: 1.7   Left: 1.71<br>Average: 1.71  |
| Nerve Diameter             | Right: 0.36   Left: 0.20<br>Average: 0.28 | Right: 0.20   Left: 0.14<br>Average: 0.17 |
| Retinaculum Thickness (cm) | Right: 0.21   Left: 0.23<br>Average: 0.22 | Right: 0.16   Left: 0.13<br>Average: 0.15 |
| CSA of All Tendons         | Right: 1.26   Left: 1.19<br>Average: 1.23 | Right: 0.96   Left: 0.96<br>Average: 0.96 |
| CSA of FDP                 | Right: 0.69   Left: 0.66<br>Average: 0.68 | Right: 0.44   Left: 0.42<br>Average: 0.43 |
| CSA of FDS                 | Right: 0.47   Left: 0.42<br>Average: 0.45 | Right: 0.32   Left: 0.32<br>Average: 0.32 |
| CSA of FPL                 | Right: 0.10   Left: 0.11<br>Average: 0.11 | Right: 0.20   Left: 0.22<br>Average: 0.21 |
| CSA of ECU                 | Right: 0.40   Left: 0.39<br>Average: 0.40 | Right: 0.14   Left: 0.16<br>Average: 0.15 |
| Third Space Thickness      | Right: 1.19   Left: 1.23<br>Average: 1.21 | Right: 0.54   Left: 0.61<br>Average: 0.58 |

Quantitative morphometric analysis of wrist structures demonstrating differences in carpal tunnel cross-sectional area, median nerve diameter, and flexor tendon bulk between the right and left sides of ATTRwt and amyloid negative subjects. Measurements included the median nerve, individual flexor tendons, the ECU, and third space thickness. Note: All values in cm<sup>2</sup> unless otherwise specified. CSA: Cross-sectional area; MN: Median nerve; FDP: Flexor digitorum profundus; FDS: Flexor digitorum superficialis; FPL: Flexor pollicis longus; ECU: Extensor carpi ulnaris; TSVM: Tenosynovium. Values represent the average of each patient's right and left wrists.

**Table 1. Quantitative Morphometric Analysis of Wrist Structures in ATTRwt compared with an Amyloid-Negative Control.** Cross-sectional areas (CSA), nerve diameter, and other structural measurements in ATTRwt compared with an Amyloid-Negative Control.

Moreover, severe tendinosis of the extensor carpi ulnaris and mild-to-moderate erosive changes of the carpal bones were observed in the ATTR subject, compared with only mild findings in the amyloid-negative subject (Table 2).

| Qualitative Features                                                                                                                                                                                                                                                                                                                                                                   | ATTRwt             | Amyloid Negative |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|------------------|
| Tenosynovium Thickness                                                                                                                                                                                                                                                                                                                                                                 | Severe             | Mild             |
| Retinaculum Thickness                                                                                                                                                                                                                                                                                                                                                                  | Moderate-to-Severe | Mild             |
| ECU Tendinosis                                                                                                                                                                                                                                                                                                                                                                         | Severe             | Mild-to-Moderate |
| Carpal Bone Erosion                                                                                                                                                                                                                                                                                                                                                                    | Mild-to-Moderate   | Mild             |
| Note: ECU: Extensor carpi ulnaris; MTR: Magnetization Transfer Ratio; Severe: Marked structural or pathological changes that are clearly abnormal and likely to impact function; Moderate: Noticeable alterations that may contribute to dysfunction but are not as severe or widespread; Mild: Minimal changes that are present but unlikely to have a significant functional impact. |                    |                  |

**Table 2. Qualitative MRI Features of the Wrist in ATTRwt and an Amyloid-Negative Control.** Subjective grading of tenosynovium thickness, retinaculum thickness, tendinosis, and bone erosion in ATTRwt and an amyloid negative control.

Corresponding magnetization transfer ratio (MTR) imaging confirmed these findings, demonstrating globally elevated ratios within the tenosynovium, flexor tendons, and median nerve compared with the amyloid-negative subject (Fig. 3).

These elevations, consistent with the T1 and PD observations, suggest increased macromolecular density in the affected tissues.

## Discussion

This case supports a growing body of evidence suggesting that MRI can serve as a valuable noninvasive tool in the assessment of amyloid-related CTS. While CTS is a common condition in the general population, its association with ATTR, is increasingly recognized as a potential early clinical manifestation. In this patient, detailed wrist MRI revealed characteristic features of amyloid infiltration, including thickened flexor tendons with striated signal changes, hyperintense tenosynovium, and severe median nerve compression, findings that align with previously reported imaging patterns of amyloid deposition. These observations underscore the utility of MRI not only for symptom evaluation but also for identifying musculoskeletal involvement in systemic amyloidosis, potentially aiding in earlier diagnosis.

While there are publications describing MRI findings in amyloidosis, there is currently no published literature describing MRI evaluation of specifically ATTR amyloidosis in the wrist. A study describing  $\beta$ 2-microglobulin amyloid deposition in the wrist [10] demonstrates imaging findings with similarities to those observed in this case. However, this area remains significantly under-researched. This gap in the literature further strengthens the rationale for the present case study, which aims to demonstrate the potential role of MRI as a non-invasive tool to promote further investigation of ATTR amyloidosis.to promote further investigation of ATTR amyloidosis.

While tenosynovial biopsy remains the reference standard for confirming amyloid deposition, it is typically reserved for more severe cases and performed at the surgeon's discretion. As a result, many patients with mild to moderate symptoms of CTS may not undergo tissue sampling or any MRI imaging, leading to missed opportunities for early diagnosis of systemic amyloidosis. In carpal tunnel patients with clinical suspicion or risk factors for amyloidosis, non-invasive wrist MRI may offer an opportunity to identify imaging features suggestive of amyloid involvement, thereby prompting targeted referral for further amyloid-specific evaluation without immediate need for invasive testing. In carpal tunnel patients with clinical suspicion or risk factors for amyloidosis, non-invasive wrist MRI may offer an opportunity to identify imaging features suggestive of amyloid involvement, thereby prompting targeted referral for further amyloid-specific evaluation without immediate need for invasive testing. Importantly, the distinct MRI findings observed in this case highlight the potential role of imaging in recognizing amyloid involvement in patients presenting with CTS who have not yet been evaluated for systemic disease. These underutilized radiologic markers, such as striated tendon signal changes, tenosynovial thickening, and nerve compression and fascicular distortion, may serve as early indicators of transthyretin amyloidosis, even in the absence of overt cardiac symptoms. In clinical practice, MRI could support decision-making around whether to pursue biopsy during carpal tunnel release surgery, helping to identify amyloid earlier and guide appropriate referral for systemic evaluation.

For qualitative assessment, a three-tier severity grading system was applied based on expert radiologic interpretation of tissue thickening and structural alteration (Table 2).

This grading scale categorizes findings as severe, reflecting marked structural or pathological changes likely to impact function; moderate, indicating noticeable alterations that may contribute to dysfunction but are not extensive; and mild, representing minimal changes unlikely to have significant functional impact. This framework was used to standardize descriptive interpretation of imaging findings in the absence of established quantitative thresholds and serves as an exploratory approach pending future validation.

Given the availability of disease-modifying therapies for ATTRwt, early identification is essential to improving patient outcomes. Although this report is limited to a single case, it highlights an imaging phenotype that warrants further investigation to determine whether specific MRI patterns can reliably suggest the presence of ATTRwt. While standard MRI can detect features such as tendon thickening, tenosynovial changes, and median nerve enlargement which may be found in other systemic disorders, the extent of thickening in addition to the integration of advanced techniques, such as MTR imaging and T1rho mapping may enhance the ability to quantify amyloid burden and differentiate ATTR-related changes from more common causes of CTS. MTR imaging assesses macromolecular content within tissue; in the context of amyloidosis, elevated MTR values may reflect increased amyloid fibril deposition, offering a noninvasive surrogate marker of disease burden [11]. Comparative and quantitative imaging approaches may help refine diagnostic criteria, offering noninvasive alternatives to tissue biopsy. T1rho mapping could help assess cartilage integrity, aiding in the understanding of amyloid infiltration processes [12]. These technical refinements not only improve diagnostic confidence

but also hold promise for future use in monitoring disease progression and therapeutic response; further investigation is currently underway to better define their clinical applicability.

In summary, this case demonstrates the potential of MRI to detect musculoskeletal involvement in ATTRwt amyloidosis and underscores its role in identifying amyloid-related CTS. These findings support the need for further research into integrating advanced musculoskeletal MRI into the diagnostic algorithm for transthyretin amyloidosis, highlighting its potential role in early detection prior to overt cardiac involvement and in guiding clinical decision-making.

## **Patient Perspective**

The patient reflected that receiving the diagnosis of systemic amyloidosis was a difficult experience for both himself and his family. Learning of the condition at 65 years of age added to the emotional weight of the diagnosis. The carpal tunnel release surgery provided meaningful symptomatic relief; however, he mentioned the improvement was temporary, as loss of mobility and intermittent pain persisted due to the severity of amyloid already present. Still, he expressed appreciation for the MRI evaluation and this study, noting that it offered a clear window into what was truly occurring within his wrists. Additionally, the imaging findings were reviewed with radiologists and physicians, who indicated that this level of detailed characterization in the early stages of disease may help enable monitoring in patients who are often undetected, particularly those with mild to moderate carpal tunnel symptoms.

He also shared that learning about this research brought him comfort, knowing that a non-invasive early detection method could help others like him whose lives are fundamentally changed by the disease. He emphasized that identifying amyloidosis earlier could enable treatments to alter the disease course, and that this possibility gave him genuine hope for future patients.

## **Declarations**

### **Author Contribution:**

All authors were involved in the case and preparation of the manuscript and/or imaging.

Ethics approval: The protocol was approved by McGill University Health Center Research Ethics Board - Centre for Applied Ethics in accordance with the International Council for Harmonisation Guideline E6 (Revision 3) on Good Clinical Practice and the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (2022).

Consent to Participate: Informed consent was obtained from the patient for participation in this study.

Consent to Publish: Informed consent was obtained from the patient for publication.

Conflict of interest: The authors declare no conflict of interests.

## Data Availability:

Qualitative MRI features of the wrist are documented in Table 2. This dataset includes descriptive features observed in MRI scans, offering insights into the qualitative aspects of wrist imaging.

Quantitative morphometric analysis of wrist structures is available in Table 1. This dataset provides detailed measurements and analysis of various wrist structures, contributing to the understanding of wrist morphology.

The data that supports the findings of this study are available from the corresponding author upon reasonable request.

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Jean-Pierre Abdallah served as the primary author of the manuscript. Marcus Saldanha contributed as a co-author, was responsible for patient recruitment, performed the MRI scans, and provided assistance in manuscript preparation.

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## Figures

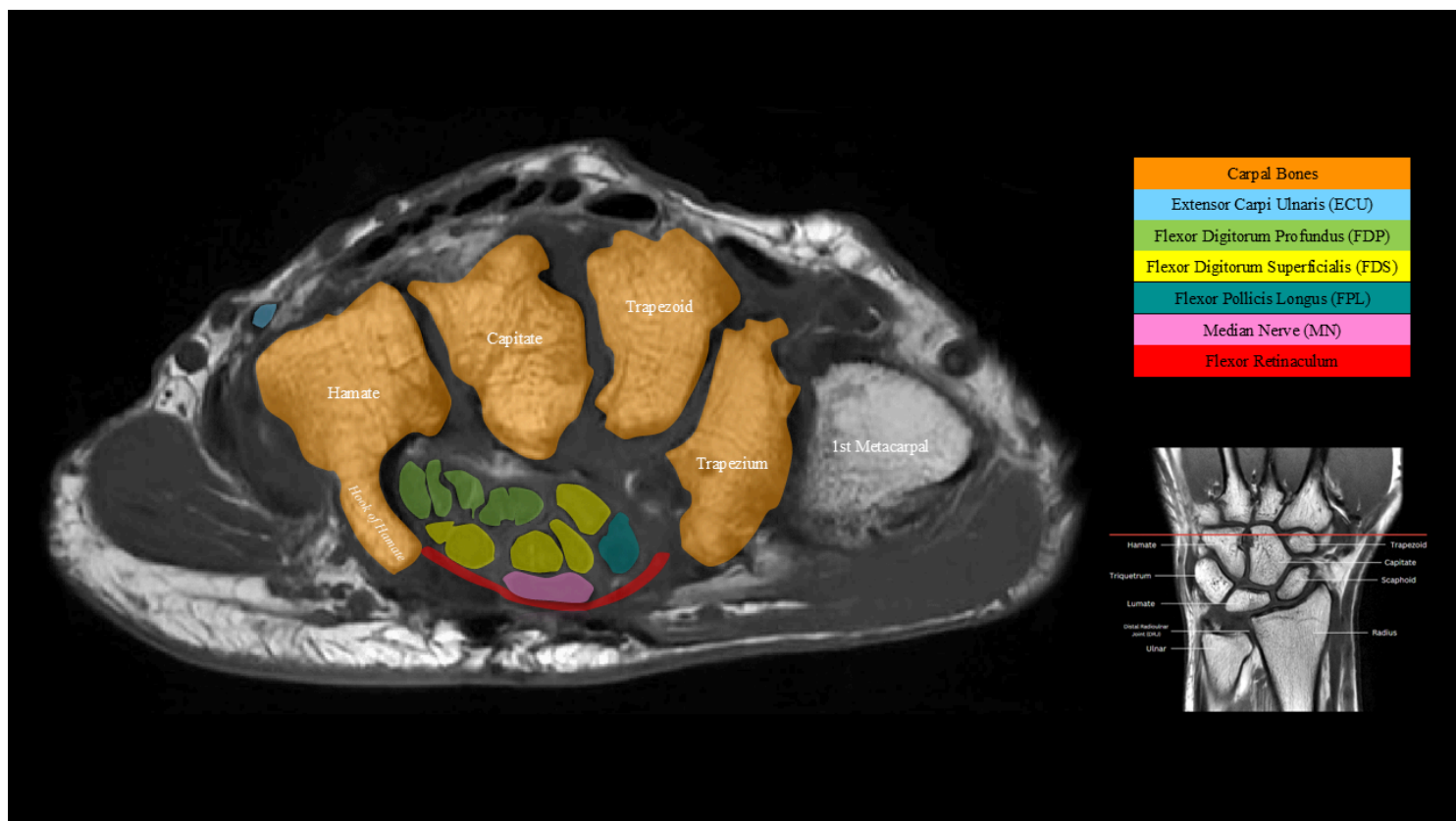


**Figure 1**

### **Annotated Axial and Coronal T1-Weighted Wrist MRI Showing Carpal Tunnel and Anatomical Structures.**

The axial view highlights the location of each anatomical structure within the carpal tunnel at the hook of the hamate, with the following color coding: carpal bones (orange), flexor digitorum profundus (FDP) tendon (green), flexor digitorum superficialis (FDS) tendon (yellow), flexor pollicis longus (FPL) tendon (teal), median nerve (pink), and flexor retinaculum (red). The extensor carpi ulnaris (ECU) tendon (light blue) is noted outside the carpal tunnel. The coronal view provides an additional perspective, showing wrist anatomy with a red line indicating the location of the hook of the hamate.

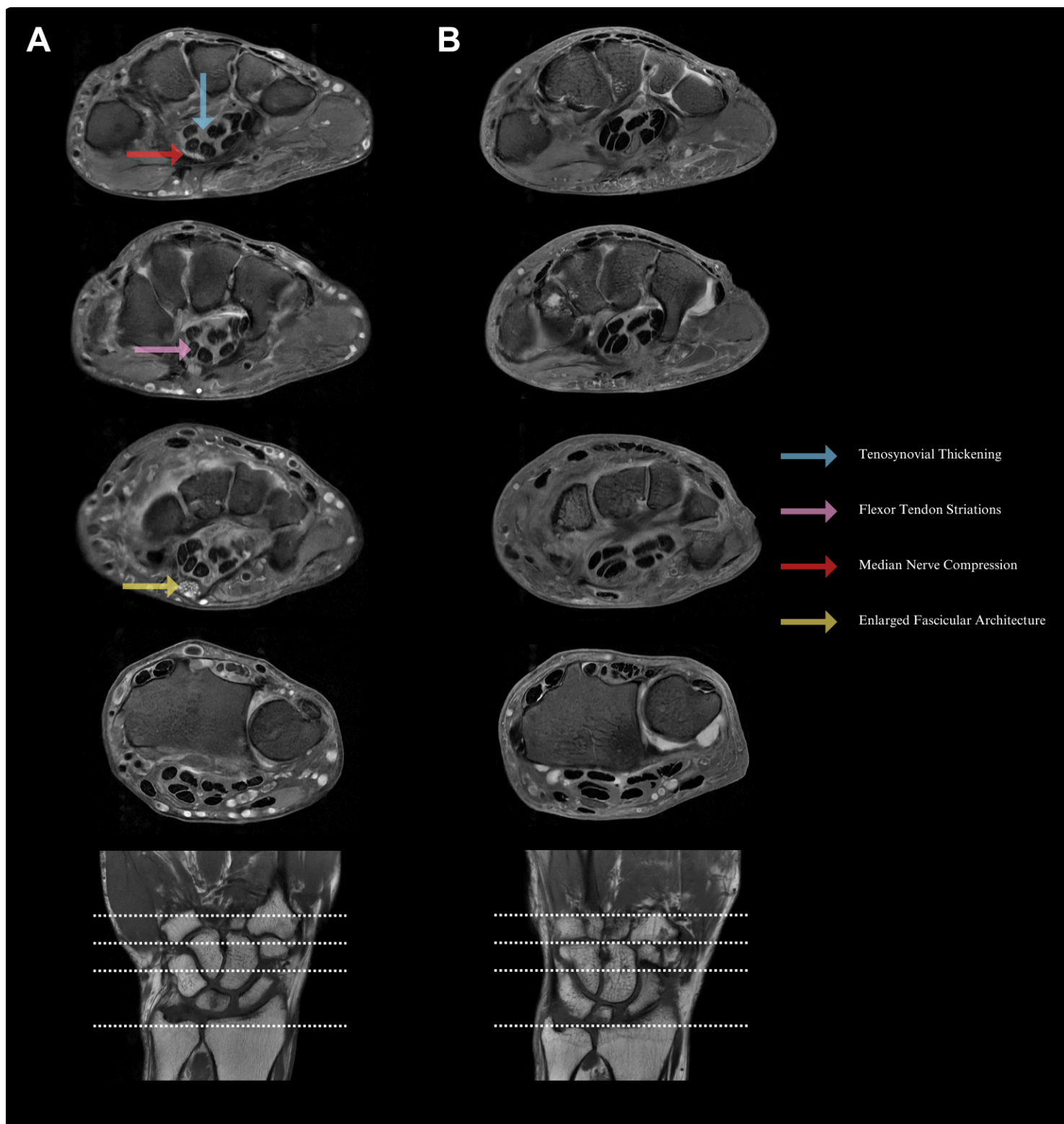


**Figure 2**

**Proton Density-Weighted Wrist MRI in ATTRwt and Amyloid-Negative Subjects.** Proton density-weighted axial images highlighting distinct features in tendon thickening, tenosynovium signal intensity, and carpal tunnel morphology between ATTR amyloidosis (A) and an Amyloid Negative Control (B).

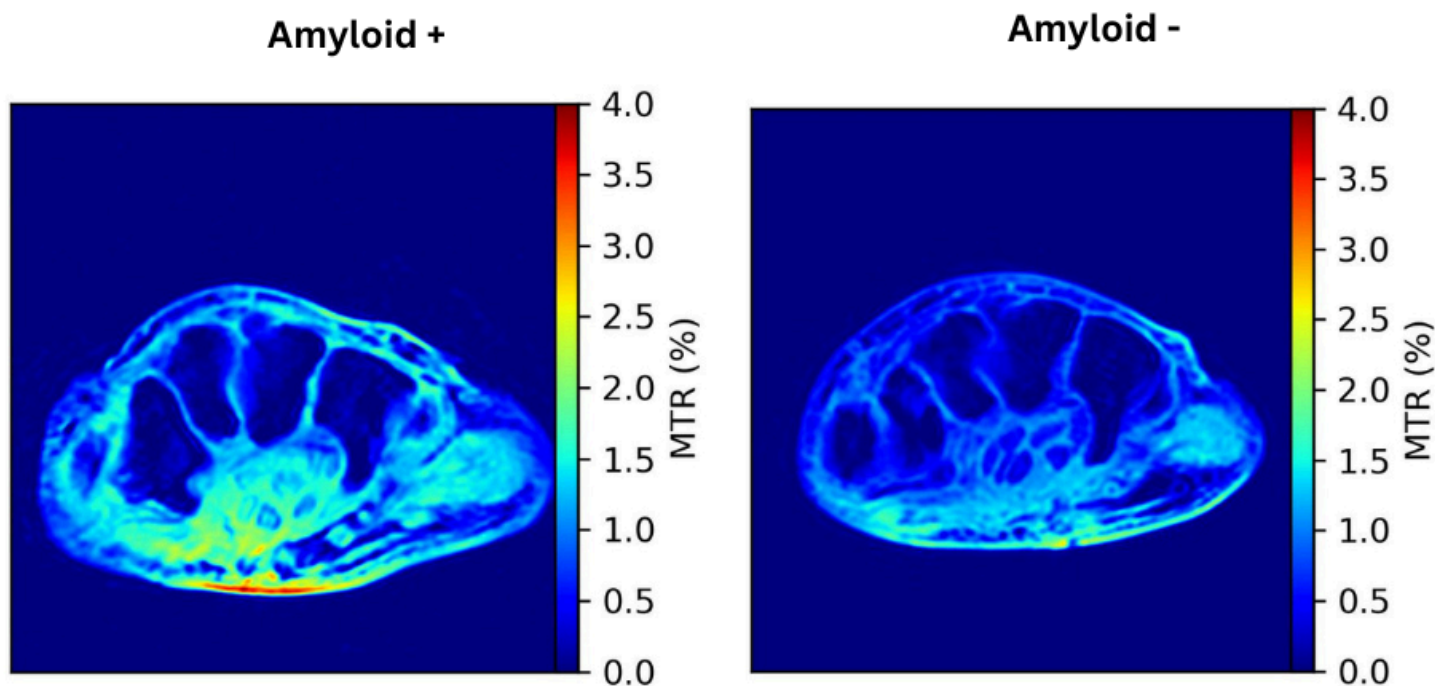


Figure 3

**Magnetization Transfer Ratio (MTR) Imaging of the Wrist in ATTR.** Axial MTR map of the wrist demonstrating elevated ratios in the tenosynovium, flexor tendons, and median nerve in the ATTR subject (Amyloid +) compared to the amyloid negative (Amyloid -) control. Increased color intensity (blue to red) reflects higher MTR values, indicating greater macromolecular density.

## Supplementary Files

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