Case Report: Amyloid Deposits in the Flexor Tenosynovium Found During Primary Carpal Tunnel Release

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ABSTRACT

A 76-year-old female previously diagnosed with flexor tenosynovitis, presented to the clinic complaining of right wrist pain and numbness in her fingers. She was seen again after a rheumatologic workup, which was negative. It was noted that there was thenar atrophy when compared to the contralateral side. She was then scheduled for carpal tunnel release surgery. During surgery, a large area of synovitis was encountered. A radical synovectomy was performed and this tissue was sent for culture and pathology. The findings were most consistent with age-related amyloidosis. One week after surgery, the patient was contacted by telephone and reported that her hand numbness and tingling had significantly improved, and she had resumed most of her daily activities. The patient was counseled regarding her pathology results and other manifestations of amyloidosis. A cardiology consult was recommended.

Keywords: Tenosynovitis; Amyloid; Carpal tunnel syndrome

INTRODUCTION

Carpal tunnel syndrome (CTS), described as the most common peripheral mononeuropathy, is a compression neuropathy of the median nerve at the wrist.[1] When evaluating a patient in a preoperative clinical setting, several patient risk factors can heighten a physician's suspicion to CTS including: diabetes, thyroid disease, obesity, and hypercholesterolemia.[2-5] Patients often complain of hand numbness that awakens them from sleep at night, positional numbness during activities such as driving, hand weakness, and loss of dexterity. Electromyography and nerve conduction studies (EMG/NCS) can be helpful in confirming the diagnosis and severity of the syndrome. Although rare, amyloid deposition in the flexor tenosynovium can sometimes be the first sign of the presence of systemic amyloidosis; the systemic type presents as amyloid fibrils formed from the monomers of a mutated, hereditary or wild-type, α-synuclein, transthyretin gene.[6] Intra-operatively, specific findings such as tissue overlying the nerve that looks unusually thickened and of white/tan color can alert the surgeon to the possibility of systemic disease. If this is suspected, tissue should be sent for pathological evaluation and the pathologist should be alerted to the possibility of amyloidosis. Classically, intraoperative findings consist of noninflammatory changes of the flexor tenosynovium. However, several histopathologic studies have demonstrated amyloid deposition in the flexor tenosynovium, with prevalence ranging from 2.0% to 19.0%.[7, 8-11] Clinical evidence of systemic amyloidosis range from skin manifestations, cardiomyopathy, musculoskeletal disease, gastrointestinal disease, renal, neurologic, and hematologic abnormalities, and pulmonary disease.[12] Therefore, it is important that surgeons are aware of this possibility as they can set in motion a life-saving comprehensive medical evaluation.

CASE REPORT

Clinical Evaluation

The patient is a 76-year-old female who presented to the clinic complaining of right wrist pain and numbness in her fingers. The patient had previously been diagnosed with flexor tenosynovitis based on magnetic resonance imaging (MRI). These symptoms had been present for several months and were interfering with her job as a writer. The patient denied any injury or inciting event. She also denied night pain. Her physical exam included finger numbness and mildly diminished sensation in a median nerve distribution. Her symptoms were reproduced with Phalen's test, Durkin's test, and with Tinel's over the carpal tunnel. She did not have numbness reproduced with elbow hyperflexion. The patient had mild swelling and fullness of the volar wrist, and tenderness to palpation in this area. The patient's hand was otherwise neurovascularly intact. Nerve conduction studies were not performed. The patient was sent for rheumatologic workup to look for an

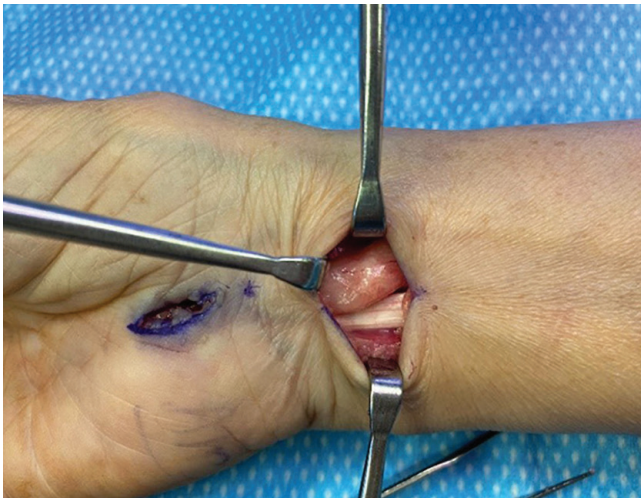

Figure 1. *Intraoperatively, the transverse carpal ligament appeared thickened. A separate incision just proximal to the flexor crease was made to evaluate the flexor tendons, where a large area of synovitis was encountered. A radical synovectomy was performed and this tissue was sent for culture and pathology. In the area of synovitis, the median nerve appeared enlarged and fascicular.*

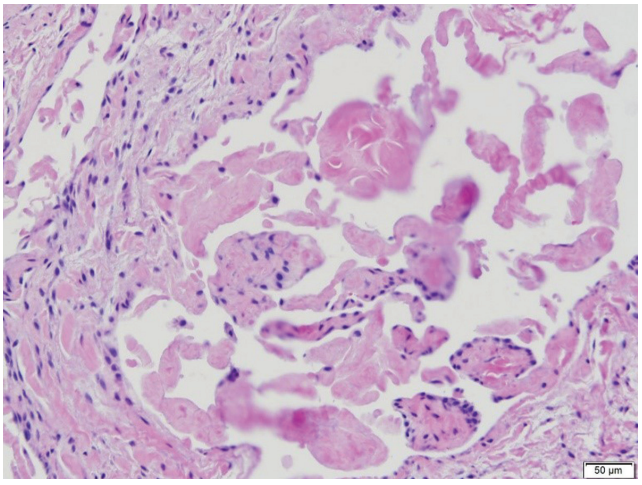

Figure 2. *H&E stain of the intraoperative biopsy, pathologically studied. The stain exhibiting red waxy material.*

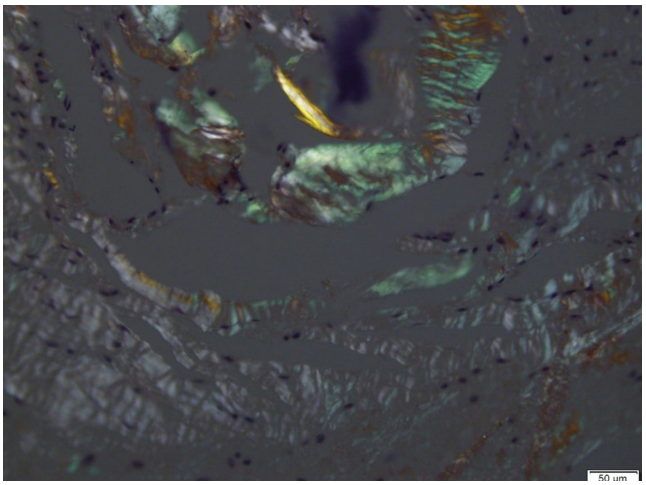

Figure 3. *Examination of the specimen under Congo Red staining under polarized light demonstrated apple green birefringence, confirming the presence of amyloid.*

etiology of her synovitis. She was seen again 2 months later to review her rheumatologic workup, which was negative for rheumatoid factor, HLA-B27, ANA, Anti-DS DNA, and Anti-CCP. The patient made some activity modifications, but her symptoms were continuing to interfere with her daily activities, and her hand numbness was affecting her sleep. At this visit, it was noted that there was thenar atrophy when compared to the contralateral side. Nonoperative management including bracing and injections were discussed; however, due to the patient's progressive symptoms and newly appreciated thenar atrophy, surgical management was recommended. She was agreeable to carpal tunnel release, and surgery was scheduled.

Imaging

Radiographic evaluation of the patient's symptomatic right wrist demonstrated diffuse soft tissue swelling consistent with tenosynovitis, and scapholunate joint widening, suggestive of a chronic scapholunate ligament injury. The patient was slightly ulnar positive, and diffuse degenerative changes were noted in the metacarpophalangeal and interphalangeal joints. MRI demonstrated flexor digitorum tenosynovitis and edema within the carpal tunnel. There were no structural abnormalities.

Intraoperative Findings

The patient underwent open right carpal tunnel release 2 weeks after her follow-up visit. Intraoperatively, the transverse carpal ligament appeared thickened. A separate incision just proximal to the wrist flexor crease was made to evaluate the flexor tendons, where a large area of synovitis was encountered. A radical synovectomy was performed and this tissue was sent for culture and pathology. In the area of synovitis, the median nerve appeared enlarged and fascicular (Figure 1), which is often encountered in compressive median neuropathy at the wrist.

Pathology

The flexor tenosynovitis underwent histopathologic evaluation. There was no evidence of an inflammatory synovitis. Hematoxylin and eosin (H&E) staining demonstrated waxy red material (Figure 2). Examination of Congo Red staining under polarized light demonstrated apple green birefringence, confirming the presence of amyloid (Figure 3). Liquid chromatography tandem mass spectrometry (LC MS/MS) was performed at Mayo Clinic Laboratories on peptides extracted from Congo-Red positive, microdissected areas of the paraffin embedded specimen. LC MS/MS detected a

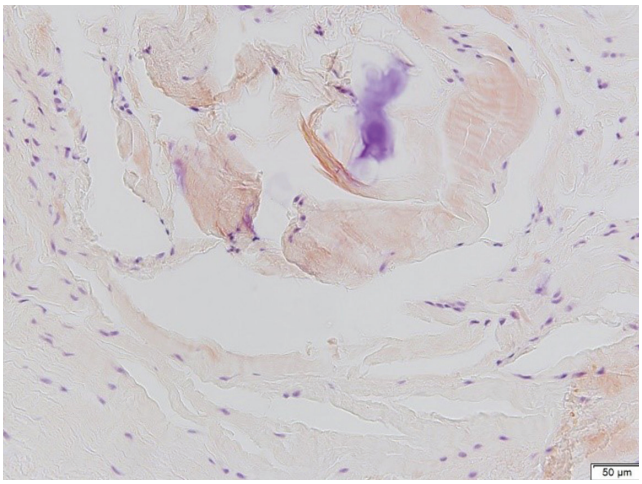

Figure 4. *Liquid chromatography tandem mass spectrometry (LC MS/MS) on peptides extracted from Congo-Red positive, microdissected areas of the paraffin embedded specimen. Congo-Red staining exhibited red material.*

peptide profile consistent with ATTR (transthyretin)-type amyloid deposition (Figure 4). LS MS/MS did not detect an amino acid sequence abnormality in the transthyretin protein. This finding is most consistent with age-related amyloidosis. Per the Mayo Clinic Laboratories' recommendations, if the clinical findings suggest hereditary transthyretin amyloidosis, sequencing this patient's TTR genes in conjunction with genetic counseling is recommended.

Postoperative Follow-Up

One week after surgery, the patient was contacted by telephone and reported that her hand numbness and tingling had significantly improved, and she had resumed most of her daily activities. The patient was counseled regarding her pathology results and other manifestations of amyloidosis. A cardiology consult was then recommended. Her night numbness and positional numbness resolved and her strength gradually improved.

DISCUSSION

The two most common systemic amyloidosis diagnoses are immunoglobulin light chain and hereditary transthyretin amyloidosis (ATTR), which can present in a variety of forms due to their effect on many systems including cardiac, renal, gastrointestinal, hematologic, and musculoskeletal.[13] One of the most severe manifestations is transthyretin amyloid cardiomyopathy and recent advances in treatment make the timing of the diagnosis paramount to early and effective treatment.[14]

The diagnosis of CTS can often precede the diagnosis of systemic amyloidosis by many years, yet the lack of awareness of this link often results in a delay in diagnosis. In 2018, a prospective study found that 10.2% of a cohort of men age > 50 years and women > 60 years old undergoing carpal tunnel release for seemingly idiopathic disease had amyloidosis diagnosed from tenosynovial tissue biopsy.[15] Furthermore, a study of patients with cardiac amyloidosis found that CTS was the presenting symptom in 16.0% of patients.[16] Hand surgeons must be aware of this link as they can set in motion a series of life-saving events.

In this case, the patient did present with symptoms of CTS, and provocative maneuvers of Phalen's and Durkin's further confirmed this diagnosis. However, her volar wrist swelling and prior diagnosis of flexor tenosynovitis was a bit unusual and heightened suspicion to other etiologies including rheumatologic diseases. Although her preoperative workup for other etiologies was negative, there are described red flag symptoms of amyloidosis in the literature. Namely, in the study by Bishop et al.,[15] the authors state that in males > 50 and females > 60 years old who present with either bilateral symptoms or persistent symptoms despite multiple prior carpal tunnel releases, amyloidosis should be considered. Additionally, computed tomography (CT) scans can confirm synovial thickening. An indication of amyloidosis may present as periarticular soft tissue involvement such as masses, absence of periarticular osteoporosis, preservation of articular space, subchondral cysts, and joint effusion and erosions.[17]

The presence of amyloid deposits from hereditary ATTR amyloidosis in the tendons and ligaments has been shown to be systemic; two studies in the past 5 years have highlighted that CTS was related to the diagnosis of wild-type ATTR amyloidosis with cardiac amyloidosis diagnosed 5 years to 9 years later.[18] Approximately 50.0% of individuals with hereditary ATTR amyloidosis develop cardiac disease; subclinical cardiac involvement (e.g., cardiomegaly on chest x-ray, thickening of the interventricular septum, and granular sparkling on echocardiography) can be used to diagnose late onset hereditary ATTR amyloidosis occurrence in the cardiovascular system.[19] However, genetic workup and gene sequencing can be used to suspect new pathogenic mutations.

CONCLUSION

The historical findings of the rarity of amyloidosis upon diagnosis of CTS may be due to the misdiagnosis, non-diagnosis, or a variety of non-disease specific presenting symptoms. As demonstrated in previous studies, age-related amyloidosis arthropathy can be diagnosed in a delayed manner. A pathological investigation into the origin of synovitis associated with CTS intraoperatively is worthwhile due to the systemic nature of hereditary ATTR amyloidosis. Genetic testing after pathologic confirmation is necessary to possibly identify and halt the progression of systemic disease.

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