JOURNAL OF PLASTIC SURGERY AND HAND SURGERY
2023, VOL. 57, NOS. 1–6, 257–262
https://doi.org/10.1080/2000656X.2022.2061498

ARTICLE

Mast cell presence in tendon sheaths of trigger fingers: implications on pathogenesis and clinical presentation

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ABSTRACT

Trigger finger is a common hand disorder; however, its pathogenesis remains unknown. In this study, we aimed to investigate mast cells, fibroblast activators that synthesize collagen, in the tendon sheaths of trigger fingers. We investigated the presence of mast cells and their association with changes in the collagen content of the tendon sheath and clinical data. We performed a multicenter prospective study of 77 adult patients with trigger finger who had undergone resection of the first annular pulley between August 2012 and January 2020. The tendon sheath was immunostained with an anti-tryptase antibody to confirm mast cell presence. The percentage of collagen in the tendon sheath was determined by picrosirius red staining observed through a polarization microscope. The clinical data, including the duration from symptom onset to surgery, severity, pain numerical rating scale, and Hand20 scores, were evaluated. Tryptase-positive mast cells were recognized in 83.5% of all specimens. The mast cell presence group (Group P) had a significantly higher percentage of type-3 collagen in the tendon sheath than the non-mast cell presence group (Group N) (Group P, 15.6%; Group N, 12.7%; $p = 0.03$). Moreover, Group P had significantly higher pain numerical rating scale (Group P; 5, Group N; 3, $p = 0.04$) and Hand20 (Group P; 35.5, Group N; 13.0, $p = 0.01$) scores than Group N. These findings suggest that mast cell presence in the tendon sheath of the trigger finger is related to the pathology and clinical symptoms of trigger finger.

ARTICLE HISTORY
Received 15 September 2021
Revised 10 February 2022
Accepted 29 March 2022

KEYWORDS
Trigger finger; mast cell; tendon sheath; pain

Introduction

Trigger finger is a type of stenosing tenosynovitis, a hand disorder caused by mechanical impingement of the flexor tendon and tendon sheath. Its main symptoms are snapping and pain which may result in restriction of flexion and extension of the fingers. The severity and the course of the symptoms vary.

Pathological studies of trigger finger and normal tendon sheaths have reported that the finger tendon sheath consists of three layers [1–3]. The outer layer is rich in blood vessels and in continuity with the synovium, the middle layer is a thick layer containing chondrocyte-like cells and fibroblasts, and the inner layer is a single or two-celled layer that abuts the flexor tendon [3]. The tendon sheath of the finger contains abundant collagen in the extracellular matrix, particularly in the middle layer [1,2]. Previous studies have shown that trigger finger tendon sheaths consist of an increased proportion of type-3 collagen, whereas normal tendon sheaths are composed mainly of type-1 collagen [4,5]. Trigger finger is also called 'stenosing tenosynovitis'; however, it exhibits poor infiltration of inflammatory cells into the tendon sheath, and the mechanism of its onset and pathology is still unclear [3].

Recently, it has been suggested that mast cells contribute to inflammation and other tissue changes in immunoglobulin E-associated (IgE-associated) allergic disorders, as well as in certain immune responses that are considered independent of IgE [6]. Mast cells have been reported to be associated with rheumatoid arthritis, and many researchers have confirmed their presence in the synovium [7]. Additionally, mast cells are involved in atherosclerosis, malignancy, arthritis, and especially fibrotic diseases such as pulmonary fibrosis. Synovial proliferation and flexor sheath fibrosis are identified as causal factors of trigger finger [8]. Hence, we hypothesized that mast cells are present in the tendon sheath of the trigger finger and may be involved in its pathology, such as fibrosis. In this study, we aimed to determine mast cell presence in the tendon sheaths of trigger fingers and identify their role through histological examination and comparisons with clinical data.

Materials and methods

Level of evidence: II

This study prospectively investigated 77 adult patients (79 specimens) who underwent resection of the first annular (A1) pulley for trigger finger at between August 2012 and January 2020. The patients (30 men and 49 women) ranged in age from 37 to 88 years (mean, 60.8 ± 10.5 years). The mean duration from the onset of symptoms to surgery was 18.1 (±18.4) months. The affected digits were 31 thumbs, 7 index fingers, 23 middle fingers, 16 ring fingers, and 2 little fingers. The trigger finger diagnosis was confirmed by a hand surgeon or an orthopedic surgeon. Consecutive patients over the age of 20 years who were able to provide written consent were included in this study. However,

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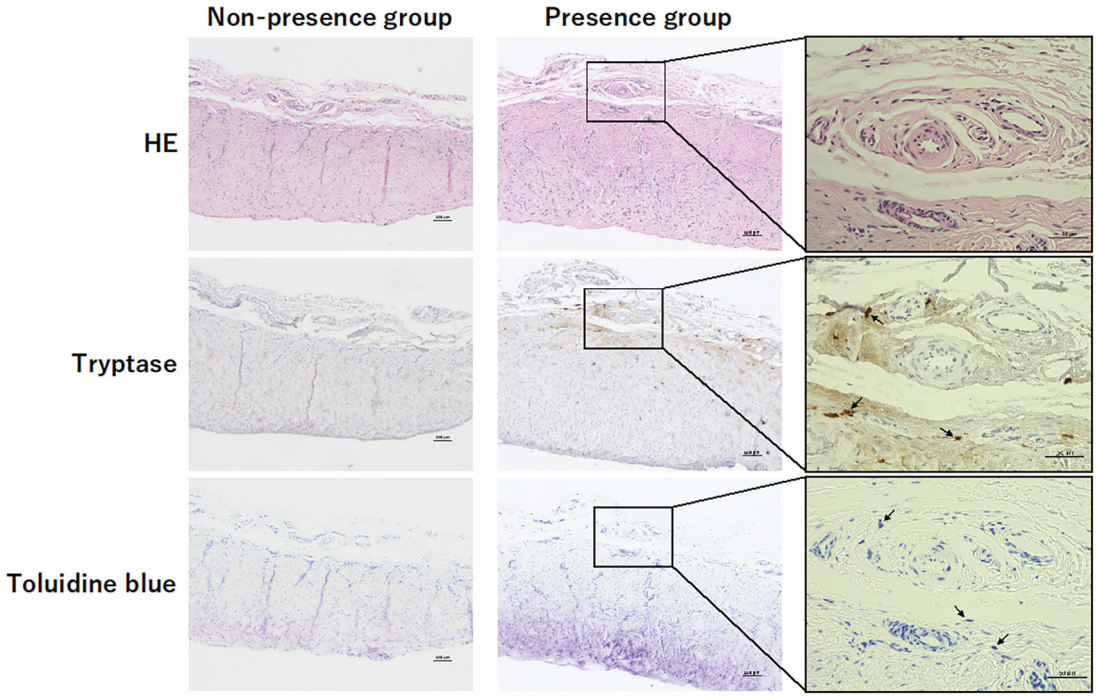

Figure 1. Presence of tryptase-positive mast cells in the outer layer of the trigger finger tendon sheath. The panels are longitudinal sections of the A1 pulley. The upper row is tissue stained with hematoxylin-eosin (HE), the middle row is tissue immunostained with anti-tryptase antibody acquiring a 3,3′-diaminobenzidine (DAB) color development, and the lower row is tissue stained with toluidine blue. As a comparison, the specimen without mast cells is shown in the left column. The middle column is the mast cell presence specimen, and the right column is an expansion. The black arrow in the expansion shows a mast cell. With anti-tryptase staining, the expression of tryptase is shown to be in and around the cells. The mast cells showing reorganization of metachromasia on toluidine blue staining.

patients with a history of thyroid disease, rheumatoid arthritis, renal failure, congenital trigger finger, post-traumatic trigger finger, and infectious flexor tenosynovitis were excluded to investigate idiopathic trigger fingers. To assess the severity of preoperative symptoms, Froimson's classification was used, and the pain numerical rating scale (PNRS) and Hand20 scores were assessed preoperatively. PNRS was calculated to evaluate the pain intensity, involving grading the pain severity from 0 to 10, with 0 representing no pain and 10 representing the most severe pain imaginable. Hand20 is a self-administered upper extremity disability evaluation questionnaire with illustrations, and the score is scaled between 0 and 100 with higher scores indicating more severe upper-extremity disability. It has previously been validated for upper extremity disorders, including trigger finger [9]. The hospital ethics committee at the institution where the study was conducted approved the study, and all patients provided informed consent before the surgery.

Histological analysis

A specimen was a sagittal section of the entire length of the tendon sheath in the center of the A1 pulley. The specimens were fixed in a 10% neutral-buffered formalin solution, embedded in paraffin, and then cut into 4-μm-thick longitudinal sections. They were dewaxed with xylene, rehydrated in stages with varying concentrations of methanol (100% to 70%), and then stained with hematoxylin and eosin (HE), toluidine blue, and picrosirius red. Furthermore, the mast cells were stained immunohistochemically using an automated staining system (VENTANA Benchmark HX Module SM; Roche Diagnostics, Risch-Rotkreuz, Switzerland) with the tryptase mouse monoclonal antibody (518-102036; Cell Marque, California, USA) against the mast cell tryptase. The tryptase antibody has been established as a sensitive and specific marker for mast cells in paraffin sections [10]. The presence of type-3 collagen was also confirmed by immunohistochemical staining. Anti-human collagen type 3 goat polyclonal antibody (1:400; #1330-01; SouthernBiotech, Birmingham, USA) was used as the primary antibody and biotinylated rabbit anti-goat immunoglobulin polyclonal antibody (1:200; E0466; DAKO, Glostrup, Denmark) was used as the secondary antibody. All specimens were observed using a BZ-X710 microscope (Keyence, Osaka, Japan). The collagen was stained with picrosirius red and observed with a polarization filter (JTP, Saitama, Japan) attached to a BZ-X710 microscope. Under a polarization microscope, type-1 collagen appears yellow, orange, or red, while type-3 collagen appears green. Collagen composition in the tendon sheath is evaluated by utilizing this characteristic [11]. A single slide with a 4-fold field of view was used to calculate the proportion of type-3 collagen per sample. The total thickness of the A1 pulley can be included in this view. Specifically, the proportion of green-stained areas in the total area of the middle layer of tendon sheath in this visual field was defined as the proportion of type-3 collagen. The digitized images were analyzed using the ImageJ version 1.51 software.

Statistical analysis

All statistical analyses were performed with Easy-R (EZR), which is a graphical user interface for R. More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics. The normal distribution of data was confirmed by the Shapiro-Wilk test ($p > 0.05$). Continuous data are shown as means with standard deviation (if normally distributed) or as medians with percentiles P_{25}–P_{75} (if non-normal). Categorical data are shown as counts with percentage. Continuous data were analyzed using Student's t-test (if normally distributed) or the Mann–Whitney U-test (if non-normal). Categorical variables were analyzed using a chi-square test or Fisher's exact test. A p value of <0.05 was considered statistically significant.

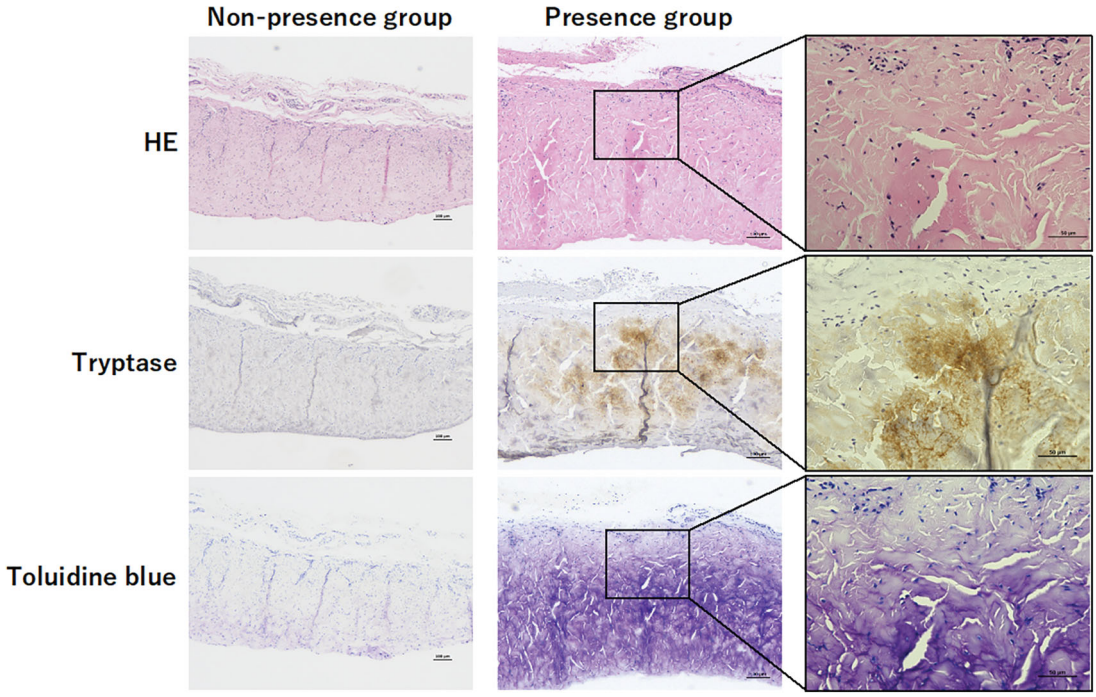

Figure 2. Presence of tryptase-positive mast cells in the middle layer of the trigger finger tendon sheath. The panels are longitudinal sections of the A1 pulley. The upper row is tissue stained with hematoxylin-eosin (HE), the middle row is tissue immunostained with anti-tryptase antibody acquiring a DAB color development, and the lower row is tissue stained with toluidine blue. In the anti-tryptase staining, diffusely expressed tryptase is recognized in the middle layer.

Results

The presence of tryptase-positive mast cells was noted in 66 specimens (83.5%), of which 39 had mast cells in the outer layer of the tendon sheath and 27 had mast cells mainly in the middle layer. When the mast cells were observed mainly in the outer layer, tryptase accumulated in and around the mast cells (Figure 1), whereas when they were present mainly in the middle layer, tryptase accumulated diffusely in the layer (Figure 2). Specimens with mast cell presence were divided into the outer-layer presence group and the middle-layer presence group; no significant differences were found between the two groups in terms of age, duration from onset to surgery, the percentage of type-3 collagen in the tendon sheath, Froimson's grades, and PNRS and Hand20 scores. However, the duration from onset to surgery tended to be longer in the middle-layer group (median 12 months) than in the outer-layer group (median 10 months) ($p = 0.08$).

To investigate the role of mast cells in the tendon sheath of trigger fingers, all specimens were divided into two groups, namely, present mast cells (Group P) and not-present mast cells (Group N). The two groups were compared with respect to their histological examination results and clinical data (Table 1). The median values of the percentage of type-3 collagen in the tendon sheath stained with picrosirius red in Group P and Group N were 15.6% and 12.7%, respectively. Additional immunostaining for type-3 collagen was performed to calibrate and confirm type-3 collagen observed under a polarization microscope with picrosirius red (Figure 3). Group P was composed of significantly higher type-3 collagen than Group N ($p = 0.03$) (Figure 4). There were no significant differences in age, the duration from onset to surgery, and Froimson's grades between the two groups. However, both PNRS and Hand20 scores were significantly higher in Group P than in Group N, indicating that the cases with mast cell presence experienced more severe pain and upper extremity disability. The median value of PNRS was 5 in Group P and 3 in Group N ($p = 0.04$), and the median value of Hand20 was 35.5 in Group P and 13.0 in Group N ($p = 0.01$).

Discussion

In this study, we investigated the presence of mast cells in the tendon sheaths of trigger fingers and their association with clinical findings. This is the first report confirming the presence of tryptase-positive mast cells in the tendon sheaths of trigger fingers. Consistent with previous reports, type-3 collagen was found in the tendon sheaths of trigger fingers, and cases in which mast cells were present in the tendon sheath had a significantly higher percentage of type-3 collagen and showed more severe pain and disability in the upper limbs.

Collagen is synthesized by mesenchymal cells such as fibroblasts. Mast cells have been shown to be a potent mitogen for fibroblasts, and mast cell-secreted tryptase has been shown to induce fibroblasts and stimulate fibroblasts to synthesize type-1 collagen [12]. It has also been shown that mast cells influence the increase in type-3 collagen in the peritoneum in chronic renal failure [13]. Moreover, multifunctional cytokines secreted by mast cells, including transforming growth factor (TGF), basic fibroblast growth factor (bFGF), interleukin 4 (IL-4), and tumor necrosis factor (TNF), have been shown to be potentially important mediators that stimulate synthesis of the extracellular matrix and increase collagen production by fibroblasts. Significant evidence that mast cells are involved in collagen synthesis has been noted. Mast cells are well known to be involved in fibrotic diseases such as hypertrophic scar, pulmonary fibrosis, glomerulosclerosis, and cirrhosis, and type-3 collagen has been reported to be overexpressed in these fibrotic diseases [14]. The proportion of type-3 collagen also increases in the trigger finger tendon sheaths [4,5]. The A1 pulleys of the trigger fingers were shown to be thicker compared to the normal A1 pulley [15,16]. Some reports have mentioned fibrosis

Table 1. Demographic appearances of Group P (presence mast cells) and Group N (not presence mast cells).

Parameter	Group P ($n = 66$)	Group N ($n = 13$)	p value
Age (years)	61.4 (10.2)	57.6 (11.8)	0.24[a]
Sex			0.22[b]
Male	23 (35%)	7 (54%)	
Female	43 (65%)	6 (46%)	
Duration from onset to surgery (months)	11.5 (5.3–24)	15.0 (6.0–24)	0.4[c]
Type-3 collagen (%)	15.6 (11.8–19.2)	12.7 (10.2–13.1)	0.03[c]
Hand20 score	35.5 (18–53)	13.0 (4–36)	0.01[c]
PNRS score	5 (3–7)	3 (1–5)	0.04[c]
Froimson's classification			0.48[d]
Grade 1	19 (29%)	1 (8%)	
Grade 2	29 (44%)	9 (69%)	
Grade 3	10 (15%)	2 (15%)	
Grade 4	8 (12%)	1 (8%)	

PNRS; Pain Numerical Rating Scale.
Data are shown as means (SD), medians (P_{25}-P_{75}), or n (%).
[a]Student's t-test.
[b]Fisher's exact test.
[c]Mann–Whitney U-test.
[d]Chi-square test.

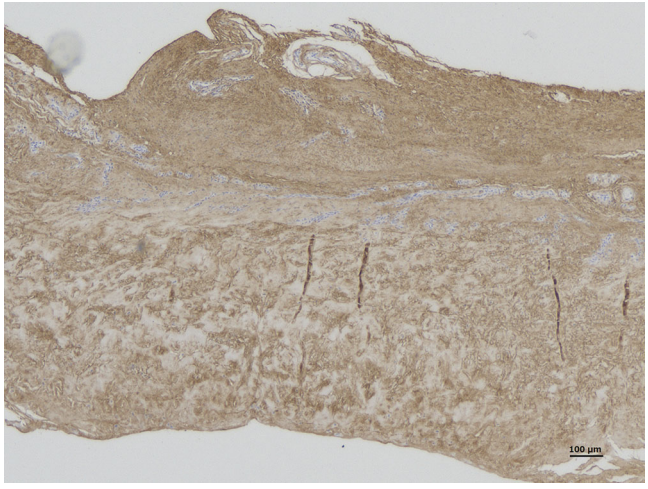

Figure 3. Immunostaining of the trigger finger tendon sheath with anti-type-3 collagen antibody.

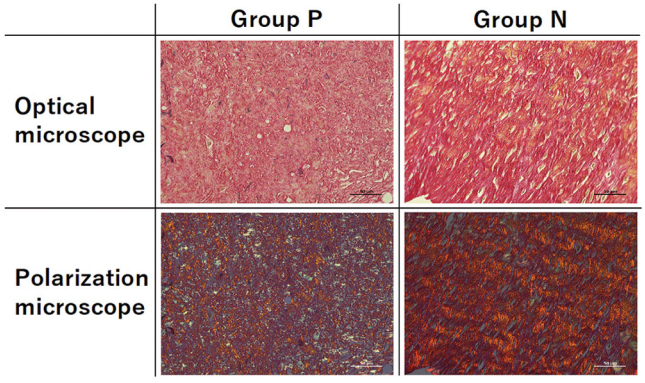

Figure 4. Trigger finger tendon sheath stained with picrosirius red. Under an optical microscope, specimens of Group P (presence of mast cells) and Group N (no presence of mast cells) show presence of red-stained collagen. Under a polarization microscope, Group P has areas of type-3 collagen stained green, whereas Group N has a smaller area of type-3 collagen.

of the tendon sheath as a causal factor of trigger finger [8,17]. The results of this study also suggest that mast cells are involved in fibrotic changes and changes in the collagen composition of the tendon sheath in cases of trigger finger.

Although the exact pathogenesis of trigger finger is still unclear, several mechanical causes have been proposed, including microtrauma from compression and friction of tendons and tendon sheaths due to repetitive finger movements [18]. Although typical mast cell activation occurs *via* aggregation and cross-linking of high-affinity IgE receptors by antigen-binding IgE antibodies leading to degranulation and release of inflammatory mediators, mast cells have been shown to be activated and degranulated under mechanical stress [19–21]. Drossos *et al.* speculated that abnormal hyperplasia of the A1 pulley of trigger fingers was caused by changes in mechanical stress along the flexor tendons [3]. Together with these findings, our results suggest that mast cells activated by changes in the mechanical environment may alter the collagen composition of the tendon sheath and contribute to fibrosis for trigger fingers.

The PNRS and Hand20 scores were significantly higher in Group P than in Group N. In recent years, the importance of interactions between the immune system and the nervous system in pain has been well-recognized. Mast cells are found near primary nociceptive neurons and considered to be involved in nociceptor sensitization in a variety of contexts [22]. Mast cell-derived mediators such as tryptase and histamine cause neuropeptides, such as substance P and calcitonin gene-related peptide, to be released from proximal nerve endings, and subsequently, substance P can further activate mast cells, allowing them to interact with the nervous system in both directions [23,24]. Previous studies have shown that enhanced mast cell degranulation and increased mast cell counts at the peripheral levels contribute to hyperalgesia in various rodent models of pain [25]. Increased numbers of mast cells in the intestinal mucosa of irritable bowel syndrome (IBS) patients compared to control individuals have been observed, and elevated tryptase levels were found in colon biopsies of IBS patients [26]. In addition, degranulating mast cells located in the proximity of colonic nerve fibers correlated with pain scores of IBS patients [27]. Chronic prostatitis-associated chronic pelvic pain syndrome patients (compared to controls) also showed increased mast cell counts and increased tryptase and nerve growth factor (NGF) content in the expressed prostatic secretion [28,29]. Although it is still unclear which chemical mediators derived from mast cells are essential for pain, these findings indicate that mast cells sensitize peripheral nociceptors. In this study, the pain was stronger in the group in which mast cells were present. These findings indicate that mast cells in the tendon sheath may also act as sensitizers for peripheral nociceptors.

The present study has some limitations. First, the sample size is relatively small. Therefore, statistical analysis may not be accurate. Secondly, the present study lacks comparison with normal controls due to difficulties of obtaining tendon sheaths from healthy subjects.

This study is the first to demonstrate the presence of tryptase-positive mast cells in the tendon sheaths of trigger fingers, suggesting their involvement in the pathology and the clinical symptoms of this condition. Further studies are needed to elucidate the exact mechanism. This preliminary study provides evidence to support larger clinical trials. Future trials should include a larger number of cases and create an environment in which healthy subjects can be secured.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Author contributions

TN and HH researched the literature and conceived the study. SK and HI were involved in protocol development and obtained ethical approval. KI, MY, and MT recruited the patients and performed data analysis. TN wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved its final version.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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