High prevalence of wild-type transthyretin deposition in patients with idiopathic carpal tunnel syndrome: a common cause of carpal tunnel syndrome in the elderly

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Summary

Carpal tunnel syndrome is the most common type of entrapment neuropathy. However, the cause of carpal tunnel syndrome remains unclear in most cases. Senile systemic amyloidosis, induced by wild-type transthyretin deposition, is a prevalent aging-related disorder and often accompanied by carpal tunnel syndrome. In this study, we measured the frequency of unrecognized wild-type transthyretin deposition in idiopathic carpal tunnel syndrome patients. One-hundred and twenty-three patients with carpal tunnel syndrome, including 100 idiopathic patients, treated by carpal tunnel release surgery were analyzed. Tenosynovial tissues obtained at surgery were analyzed by Congo red and immunohistochemical staining. If staining for transthyretin was positive, the entire *TTR* gene was analyzed by direct DNA sequencing. We also analyzed tenosynovial tissues from 32 autopsy cases as controls. Thirty-four (34.0%) patients with idiopathic carpal tunnel syndrome showed amyloid deposition in the tenosynovial tissue, and all amyloid showed specific immunolabelling with anti-transthyretin antibody. Direct DNA sequencing of the entire *TTR* gene did not reveal any mutations, indicating that all amyloid deposits were derived form wild-type transthyretin. Statistical analysis using logistic regression showed that the prevalence of transthyretin deposition in the idiopathic carpal tunnel syndrome group was significantly higher than that in controls (odds ratio 15.8, 95% CI 3.3–75.7), and age and male gender were independent risk factors for transthyretin amyloid deposition. Our results demonstrate that wild-type transthyretin deposition is a common cause of carpal tunnel syndrome in elderly men. It is likely that many patients develop carpal tunnel syndrome as an initial symptom of senile systemic amyloidosis.

1. Introduction

Carpal tunnel syndrome (CTS), the most common form of entrapment neuropathy, is estimated to occur in 3.8% of the general population [1], and its burden on society from lost productivity is substantial [2]. CTS accompanies various conditions and diseases, including pregnancy, obesity, diabetes, rheumatoid arthritis, sarcoidosis, purulent tenosynovitis, tuberculosis, systemic lupus erythematosus, hypo- or hyperthyroidism, gout and amyloidosis. However, its aetiology remains largely unclear in most patients and idiopathic CTS is the most common diagnosis [3]. Traditionally, idiopathic CTS was believed to be caused by an incompatibility between the size of the median nerve and the contents of the carpal tunnel, leading to increased pressure within the carpal tunnel and disturbance of blood flow to the median nerve [4]. However, recent magnetic resonance imaging (MRI), histological and biomechanical studies have strongly suggested that the development of idiopathic CTS is closely related to abnormalities of the synovial tissue within the carpal tunnel, although previously reported microscopic changes were nonspecific and inconclusive.

Senile systemic amyloidosis (SSA), induced by wild-type transthyretin (TTR) deposition [5], is a prevalent aging-related disorder, as about 25% of people over age 80 have TTR deposition in the heart [6], but it is usually detected by microscopic examination at autopsy. Although SSA is usually associated with cardiac disease, such as congestive heart failure and atrial fibrillation [7], TTR deposition is not limited to the heart and is found in systemic organs, including the aorta, lung, gastrointestinal tract, liver, kidney and connective tissues [6, 8]. CTS is one of the most common clinical manifestations of SSA and often precedes cardiac

symptoms [9-11].

The prevalence of amyloid deposition in CTS patients has been investigated in a small number of studies [12-14]. However, the prevalence of wild-type TTR deposition in idiopathic CTS patients, as well as the clinical characteristics of CTS patients with wild-type TTR amyloid deposition remains unknown, since none of these studies analyzed the sequence of the *TTR* gene. Furthermore, the significance of TTR amyloid deposition for the onset of CTS is unclear due to the lack of controls. Here, we examined the frequency of wild-type TTR deposition in tenosynovial tissue in a cohort of 100 patients with idiopathic CTS by immunohistochemical staining with a highly specific and sensitive anti-TTR antibody and molecular diagnostic techniques.

2. Materials and Methods

2.1. Patients

From February 2008 to October 2010, 123 consecutive patients (31 male, 92 female) who were diagnosed with CTS and subsequently underwent carpal tunnel release surgery from three different clinical departments in Nagano Prefecture, Japan, were enrolled prospectively in this case-control study. We collected blood samples of and clinical information on these patients including body mass index (BMI). We also obtained tenosynovial tissues from CTS patients at carpal tunnel release surgery. This study was approved by the Ethical Committee of Shinshu University School of Medicine and written informed consent was obtained from each patient. CTS was diagnosed based on the patients' clinical history, physical examination,

nerve conduction studies and MRI of the wrist. Physical examinations included the Tinel-like sign at the wrist, Phalen test and sensory disturbance detected over the median nerve-innervated area. To study only idiopathic CTS, we excluded the following conditions: pregnancy, rheumatoid arthritis, multiple myeloma, M-protein in the serum and urine, chronic renal failure under haemodialysis, diabetes mellitus, gout, gigantism, hypothyroidism, Colles' fracture, space-occupying lesions, chondrocalcinosis, osteoarthritis, tuberculous synovitis and previously diagnosed systemic amyloidosis, including familial amyloid polyneuropathy (FAP) and SSA. MRI was used to confirm that the patients did not have any space-occupying lesions or anatomical abnormalities, such as palmaris profundus or persistent median artery.

One-hundred of 123 patients were diagnosed with idiopathic CTS and analyzed in this study. The study population (idiopathic CTS patients) consisted of 26 men and 74 women ranging in age from 40 to 92 years (average age 67.3 ± 12.1 years). As controls, we also analyzed tenosynovial tissues from 32 autopsy cases (14 men and 18 women, average age 85.8 ± 8.4 years) without history of CTS. When synovial tissue was harvested from within the carpal tunnel, the median nerve configuration at the wrist was carefully observed to determine if there was any compressive deformity at the hook of the hamate level or enlargement of the median nerve at the proximal carpal tunnel. These deformations of the median nerve were typical findings of idiopathic CTS. None of the 32 autopsy cases had such findings. Since age and sex distribution were considerably different between CTS patients and controls, we employed logistic regression analysis to correct these differences (see **2.4. Statistical analysis**).

2.2. Congo red and immunohistochemical analysis

Tenosynovial tissues obtained at surgery were analyzed by Congo red and immunohistochemical staining. The degree of amyloidosis was divided into three categories and evaluated semiquantitatively [12, 13]: grades I, II and III had mild, moderate and severe amyloid deposition, respectively. Detailed definition of grading and clinical implications are summarised in Table 1.

Immunohistochemical analysis was performed as follows. After deparaffinisation, sections were treated with Peroxidase-Blocking Solution (Dako, Glostrup, Denmark) to inhibit endogenous peroxidase activity and with Protein Block, Serum-Free (Dako, Carpinteria, CA, USA) to inhibit nonspecific binding. Anti-λ (118-134), anti-κ (116-133) [15], anti-AA [16] and anti-TTR (115-124) [17] antibodies were applied to the sections as primary antibodies for 30 min at room temperature. The sections were then incubated with EnVision+ (Dako) as the secondary antibody for 30 min at room temperature. Immunoreactivity was visualized with DAB+ (Dako).

2.3. Mass spectrometry and DNA analysis

If staining for TTR was positive, matrix-assisted laser desorption ionization/time-of-flight (MALDI/TOF) mass spectrometric analysis of immunoprecipitated serum TTR molecules and direct DNA sequencing of entire *TTR* gene were performed to detect variant forms of TTR protein and *TTR* gene mutations.

2.4. Statistical analysis

Statistical comparisons were performed between patients with idiopathic CTS and control subjects and between idiopathic CTS patients with and without TTR amyloid deposition. Logistic regression analysis was used to test the significance of TTR amyloid deposition for the onset of idiopathic CTS and to predict the independent risk factors for TTR amyloid deposition in idiopathic CTS patients. In logistic regression analysis between patients with idiopathic CTS and controls, the TTR amyloid deposition was set as a predictor (dependent variable), and age and sex were defined as independent factors or covariates. In the logistic regression analysis between idiopathic CTS patients with and without TTR amyloid deposition, one of three variables, age, sex or BMI, was set as a predictor and the other variables were defined as independent factors or covariates. We also compared demographic data of idiopathic CTS patients with TTR amyloid deposition to those without TTR amyloid deposition using the χ^2 test (for binary outcomes) or Mann-Whitney U test (for continuous variables). All statistical analyses were conducted using SPSS version 14.0J software (SPSS Inc., Chicago, IL, USA). The critical values for significance were set at $P < 0.05$ or 95% confidence interval (CI) does not overlap 1.

3. Results

3.1. Prevalence of TTR amyloid deposition in the idiopathic CTS patients

Table 2 shows demographic and histopathological data for idiopathic CTS patients and

control subjects. Thirty-four of 100 (34.0%) patients with idiopathic CTS showed amyloid deposition in the tenosynovial tissue, and all amyloid deposits were specifically immunolabelled only with the anti-TTR antibody (Fig. 1). Semiquantitatively, TTR amyloid grade I was present in 9 cases (Fig. 2A, B), grade II in 10 cases (Fig. 2C, D) and grade III in 15 cases (Fig. 2E, F). On the other hand, only 7 (21.9%) of the 32 individuals showed TTR amyloid deposition in the tenosynovial tissue in the control group and none of them had grade III amyloid deposition (Table 2). Statistical analysis by binomial logistic regression, corrected for age and sex, showed that the prevalence of TTR amyloid deposition in the idiopathic CTS group was significantly higher than that in the control group (odds ratio 15.8, 95% CI 3.29 – 75.7, Table 3). Furthermore, the prevalence of TTR amyloid deposition grade II (moderate deposition) and grade III (severe deposition) in idiopathic CTS group were particularly high compared to that in the control group with an odds ratio of 18.5 and 1.50×10^9, respectively (Table 4), suggesting that considerable deposition of TTR amyloid was closely associated with the onset of CTS.

3.2. Risk factors for TTR amyloid deposition

In the idiopathic CTS group, the average age of patients with TTR amyloid deposition was 75.1 ± 8.9 years, whereas that of patients without TTR amyloid deposition was 63.3 ± 11.5 years (Table 5). The prevalence of TTR deposition separated by age was as follows: 0/6 (0%) in the 40- to 49-year-old group, 3/24 (12.5%) in the 50- to 59-year-old group, 6/23 (26.1%) in the 60- to 69-year-old group, 14/29 (48.3%) in the 70- to 79-year-old group, and 11/18

(61.1%) in those over 80 years old (Fig. 3A). Statistical analysis by logistic regression showed that age is an independent risk factor for TTR deposition and odds ratio per 1-year increase was 1.14 (95% CI 1.06 – 1.23). The prevalence rates of TTR amyloid deposition in males and females were 17/26 (65.4%) and 17/74 (23.0%), respectively, as shown in Fig. 3B and 3C. The sex ratio of 17:17, the ratio of males to females in the idiopathic CTS with TTR amyloid deposition group, was significantly higher than that in the idiopathic CTS without TTR amyloid deposition group (9:57, Table 5). Statistical analysis by logistic regression showed that male gender was an independent risk factor for TTR amyloid deposition with an odds ratio of 11.0 (95% CI 2.67 – 45.5). There were no statistically significant differences in the affected side or BMI between idiopathic CTS patients with and without TTR amyloid deposition (Table 5).

3.3. Sequences of TTR protein and gene

Serum TTR protein and the *TTR* gene were analyzed in 29 of the 34 idiopathic CTS patients with TTR amyloid deposition. Variant TTR protein and *TTR* gene mutation were not detected by MALDI/TOF mass spectrometry and DNA sequencing in each patient, indicating that all cases of amyloid deposition were derived form wild-type TTR. No idiopathic CTS patients with TTR amyloid deposition had symptoms or signs indicative of systemic amyloidosis including cardiomyopathy, or a family history of amyloidosis.

4. Discussion

The amyloidoses are a large group of postsecretory protein misfolding and deposition diseases.[18] There are over 20 secreted human proteins whose misfolding and misassembly outside the cell is linked to amyloidosis [19]. CTS could appear as an initial symptom in long-term haemodialysis-related (β_2-microglobulin) amyloidosis, amyloid light chain (AL) amyloidosis, and TTR-related amyloidosis [12-14, 20, 21]. Misfolding of variant TTR induces the autosomal dominant genetic disorder, FAP [20-22]. while misfolding of wild-type TTR leads to the sporadic amyloid disease, SSA, which usually affects people over 80 years of age [5, 6].

The prevalence of amyloid deposition in CTS patients has been investigated in a small number of studies. Stein et al. [12] studied 140 biopsies from 108 CTS patients with various background diseases and found amyloid deposition in 23 patients (27 wrists) and TTR-related amyloid was present in 16 of these 27 cases. Nakamichi et al. [13] studied 135 biopsies from 108 idiopathic CTS patients and showed that 10 patients (15 wrists) had mild or moderate amyloid deposition in the tenosynovial tissues and TTR-related amyloid was present in 6 patients (9 wrists). On the other hand, Kyle et al. [14] performed immunohistochemical analyses of 35 CTS patients with local amyloid deposition and showed that 33 had tissue that reacted with TTR antiserum. These results suggest that TTR amyloid deposition may be a common cause of idiopathic CTS. However, the prevalence of wild-type TTR deposition in idiopathic CTS patients, as well as the clinical characteristics of CTS patients with TTR amyloid deposition remain unknown, due to patient selection bias, contamination of secondary CTS, and insufficient sensitivity and specificity of antibodies. In addition, neither

the sequence of the TTR protein nor its gene has been reported. Furthermore, the significance of TTR amyloid deposition for the onset of CTS is unclear due to the lack of controls.

Unselected idiopathic CTS patients were enrolled in this study, and we analyzed the prevalence of wild-type TTR amyloid deposition by immunohistochemical staining with a highly sensitive and specific anti-TTR antibody and molecular diagnostic techniques. In the present study, the frequency of TTR amyloid deposition on tenosynovial tissues was 34.0% (65.4% in males and 23.0% in females), which was much higher than previously reported frequencies of 11.4% (16/140) [12] and 6.7% (9/135) [13], respectively. This discrepancy is likely due to differences in study populations and sensitivity of anti-TTR antibodies. Most patients analyzed by Nakamichi et al. [13] were middle-aged women (5 men and 103 women; mean age, 56 years old), whose frequency of TTR amyloid deposition was relatively low in our study (Fig. 3C). In addition, their immunostaining results were ambiguous, as amyloid protein was not determined in many patients [13], suggesting insufficient sensitivity of antibodies. While all amyloid deposits reacted specifically with anti-TTR antibody in our study, Stein et al. [12] found many CTS patients with non-TTR amyloid deposition, as they enrolled patients with previously diagnosed systemic amyloidoses, including β_2-microglobulin amyloidosis, AL amyloidosis and AA amyloidosis. The findings of our case-control study showed that the prevalence of TTR deposition in the idiopathic CTS group was significantly higher than that in the controls (Table 3). Furthermore, the severity of amyloid deposition was closely associated with the onset of CTS (Table 4), suggesting that TTR amyloid deposition is a common cause of CTS, especially in elderly men.

There are two likely hypotheses for the pathogenesis of wild-type TTR deposition in the tenosynovial tissue. The first is that TTR amyloid deposition is a result of mechanical wear and degeneration of the tendons and the surrounding synovium during everyday activities, which are believed to play important roles in the development of idiopathic CTS. It is also likely that TTR amyloid deposition facilitates degeneration of tenosynovial tissue, which then leads to a vicious circle. In fact, Kyle et al. [23] suggested that amyloid may be localized to the tenosynovium based on a retrospective review of 124 CTS patients with local amyloid deposition. Alternatively, TTR amyloid deposition on tenosynovial tissue may be part of systemic wild-type TTR amyloidosis, SSA, as all TTR amyloid is derived from circulating serum TTR. Actually, about half of the 10 patients with SSA previously diagnosed in our department developed CTS as an initial symptom [9-11]. Considering these findings and the observation that about 25% of people over age 80 have TTR deposition in the heart [6], it is reasonable to assume that most CTS patients with wild-type TTR deposition have a small amount of TTR amyloid deposition in systemic tissues, including the heart. However, it is likely to take time to accumulate sufficient amounts of amyloid to develop cardiac symptoms. Similarly, patients with wild-type TTR-related cardiomyopathy, SSA, may have TTR amyloid deposition in tenosynovial tissue, even when they do not have CTS symptoms.

In summary, wild-type TTR amyloid deposition is commonly observed in the synovial tissue inside the carpal tunnel in elderly male patients with idiopathic CTS. It is likely that many patients develop CTS as an initial symptom of SSA. Long-term follow-up of patients with wild-type TTR deposition in the tenosynovial tissue is necessary to elucidate the clinical

picture of SSA.

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Figure Legends

Fig. 1 Histopathological findings of tenosynovial tissue from the carpal tunnel. Congo red staining showed amyloid deposits in the connective tissues (A; B, under polarized light) and all these deposits were specifically immunolabelled with an anti-TTR antibody (C–F; Immunohistochemical staining with anti-TTR (C), anti-κ (D), Anti-λ (E) and anti-AA (F) antibody). A 77 year-old woman, grade II.

Fig. 2 TTR amyloid deposition on tenosynovial tissue. Top row (A, C, E) shows Congo red staining. Bottom row (B, D, F) shows immunohistochemical staining with anti-TTR antibody. (A, B) A 76-year-old man, grade I. (C, D) A 66-year-old woman, grade II. (E, F) an 81-year-old man, grade III.

Fig. 3 Prevalence of TTR deposition in idiopathic CTS patients separated by age and sex. (A) All idiopathic CTS patients ($n=100$), (B) male idiopathic CTS patients ($n=26$) and (C) female idiopathic CTS patients ($n=74$). Data are expressed as relative percentages, with the number of patients TTR-positive and number of patients tested in each age group indicated above each bar. Statistical analysis by logistic regression showed that age (odds ratio per 1-year increase 1.14, 95% CI 1.06–1.23) and male gender (odds ratio 11.0, 95% CI 2.67–45.5) are independent risk factors for TTR deposition.

Table 1. Definition of amyloid deposition grades and clinical implications.

Grade	Definition	Clinical implications
I (mild)	Small amount of TTR amyloid deposition (ϕ < 100 μm) in some parts of biopsied tissue	Probably not related to the onset of CTS
II (moderate)	Considerable deposition of TTR amyloid ($\phi \geq$ 100 μm) in many parts of biopsied tissue	Probably related to the onset of CTS
III (severe)	Massive deposition of TTR amyloid in most parts of biopsied tissue	Probably direct cause of CTS

Table 2. Prevalence of TTR amyloid deposition in idiopathic CTS patients and controls (autopsy cases)

			Idiopathic CTS group		Control group (autopsied patients)	
Number of individuals			100		32	
Age (mean ± SD)			67.3 ± 12.1		85.8 ± 8.4	
Sex (male : female)			26:74		14 : 18	
TTR amyloid deposition	–		66/100	(66.0%)	25/32	(78.1%)
	+		34/100	(34.0%)	7/32	(21.9%)
	grade	I	9/100	(9.0%)	4/32	(12.5%)
		II	10/100	(10.0%)	3/32	(9.4%)
		III	15/100	(15.0%)	0/32	(0%)

Table 3. Logistic regression analysis between idiopathic CTS patients and controls

					Exp (B)	95% CI of Exp(B)	
Parameter	B	SE B	Wald	*P*	(Odds ratio)	Lower	Upper
Age	-0.246	0.051	23.389	<0.001	0.782	0.708	0.864
Sex	1.757	0.761	5.335	0.021	5.793	1.305	25.721
TTR amyloid deposition	2.759	0.800	11.907	0.001	15.788	3.294	75.684
Constant	18.173	3.764					

R^2= 0.67 (Nagelkerke), Model: $\chi^2(3)=78.9$, P<0.001

B, unstandardized coefficient; SE B, standard error of B

Table 4. Logistic regression analysis between idiopathic CTS patients and controls separated by TTR amyloid deposition grade

					Exp (B)	95% CI of Exp(B)	
Parameter	B	SE B	Wald	*P*	(Odds ratio)	Lower	Upper
Age	-0.237	0.051	21.729	<0.001	0.789	0.714	0.871
Sex	1.896	0.773	6.010	0.014	6.659	1.462	30.321
TTR amyloid deposition			8.460	0.037			
Grade I	2.105	0.907	5.393	0.020	8.210	1.389	48.531
Grade II	2.917	1.180	6.106	0.013	18.486	1.828	186.925
Grade III	21.130	9,330	0.000	0.998	1.502×10^9		
Constant	17.423	3.767					

R^2= 0.69 (Nagelkerke), Model: $\chi^2(3)=19.7$, $P<0.001$

B, unstandardized coefficient; SE B, standard error of B

Table 5. Characteristics of patients with idiopathic CTS with and without TTR amyloid deposition

	Idiopathic CTS with TTR amyloid deposition	Idiopathic CTS without TTR amyloid deposition	*P*
Age (mean ± SD)	75.1 ± 8.9	63.3 ± 11.5	2.6×10^{-6} *
Sex (male : female)	17 : 17	9 : 57	8.6×10^{-6} **
BMI (mean ± SD)	23.8 ± 3.7	23.4 ± 5.0	0.41 *
Location of CTS (right : left)	26 : 8	39 : 27	0.08 **

P-values were obtained using *Mann-Whitney U test (for continuous variables) or **χ^2 test (for binary outcomes).

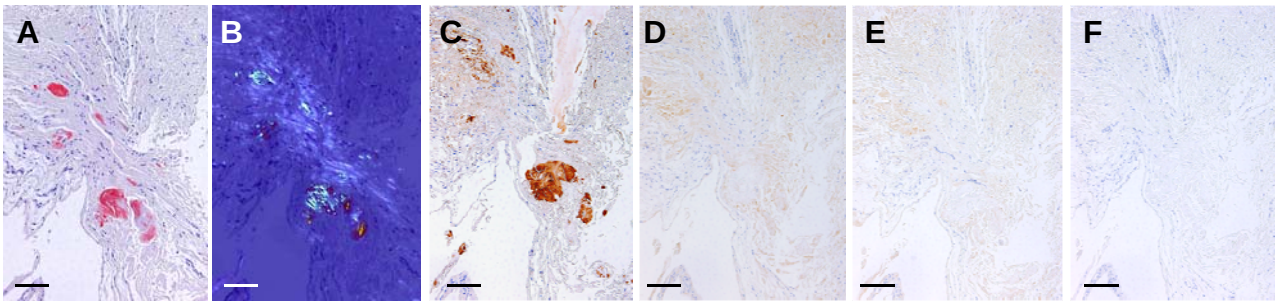

Figure 1
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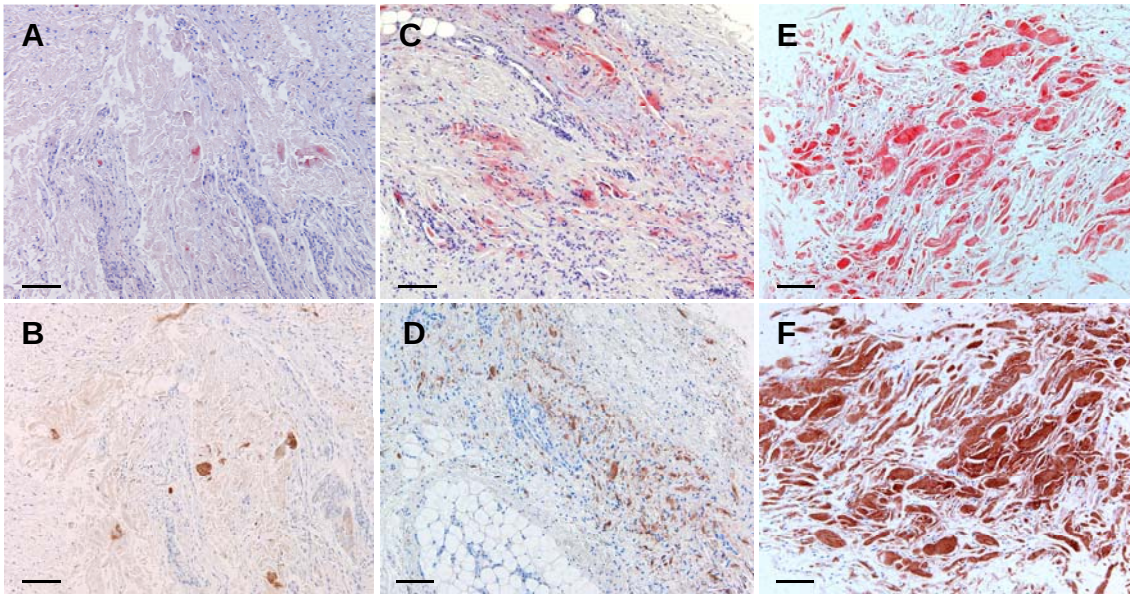

Figure 2
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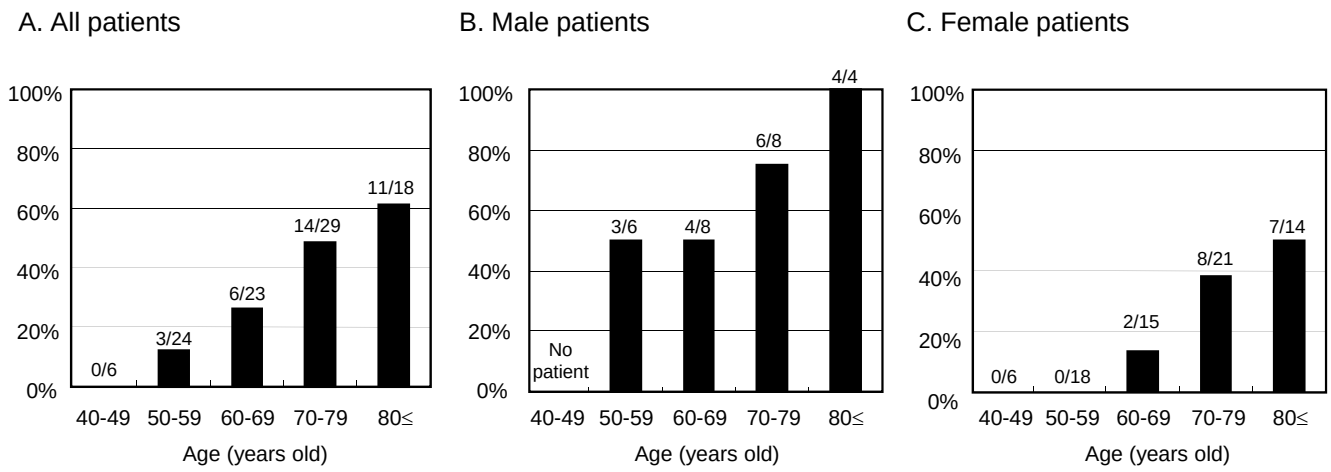

Figure 3
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