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Abstract

The results of the histological examinations of specimens of the tenosynovium of the flexor tendon, the epineurium and the transverse carpal ligament from two groups of Japanese patients with carpal tunnel syndrome (idiopathic and hemodialysis) were compared. Amyloid deposits, positively identified as β_2-microglobulin, appeared in all patients in the long-term hemodialysis group, but in no patients in the idiopathic group. Although the pathogenesis differed between the two groups, both resulted in nerve compreion in the carpal tunnel. Therefore, surgical release is considered beneficial for both groups.

KEYWORDS: carpal tunnel syndrome, histopathology, clinical results, idiopathic, hemodialysis

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Histopathology and Clinical Results of Carpal Tunnel Syndrome in Idiopathic Cases and Hemodialysis Patients

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The results of the histological examinations of specimens of the tenosynovium of the flexor tendon, the epineurium and the transverse carpal ligament from two groups of Japanese patients with carpal tunnel syndrome (idiopathic and hemodialysis) were compared. Amyloid deposits, positively identified as β_2-microglobulin, appeared in all patients in the long-term hemodialysis group, but in no patients in the idiopathic group. Although the pathogenesis differed between the two groups, both resulted in nerve compression in the carpal tunnel. Therefore, surgical release is considered beneficial for both groups.

Key words: carpal tunnel syndrome, histopathology, clinical results, idiopathic, hemodialysis

Carpal tunnel syndrome (CTS) is a compression of a median nerve resulting from a relative stenosing of the carpal tunnel induced by various pathological conditions (1, 2). Pathogenesis of many cases of CTS is not clear. In such cases, it is termed idiopathic CTS. Nevertheless, its histological occurrence is relatively common (3). Recently, long-term hemodialysis has become better known as a cause of CTS after an initial report by Warren (4).

Few of the many published reports on the histopathology of CTS have compared idiopathic CTS (I-CTS) and long-term hemodialysis related CTS (HD-CTS) cases (5). In this study, a variety of tissue specimens from both groups were taken during surgery, and the histological findings of each group were compared. The pathological conditions, clinical grade and surgical results of both groups were also compared with each histological grading.

Materials and Methods

All of the specimens examined in this study were obtained during the period when open surgery was the preferred technique for treatment of CTS at Okayama University Medical School. We began using an endoscopic surgical technique, the Okutsu's method (6), in September, 1993. Since September, 1994, only limited needle biopsy specimens have been available for comparison. Occasionally, larger specimens will continue to be available from Japanese cadavers and amputations, but diagnosis and follow-up is expected to be quite difficult.

Histological findings of CTS were studied in specimens from 55 patients with I-CTS and HD-CTS, whom we treated surgically between September, 1989, and September, 1993 (Table 1). There were 36 cases of I-CTS (a total of 40 hands), including 3 men and 33 women aged 30 to 82 years (average, 57.7 years). The diagnosis of I-CTS was made according to Schuind's criteria (3) which clearly distinguish I-CTS from other causes, such as arthritic changes, hemodialysis, Kienböck's disease, or rheumatoid arthritis.

Nineteen patients (a total of 28 hands) had been on hemodialysis from 9 to 20 years (average, 15.4 years). This group included 9 men (a total of 13 hands) and 10 women (a total of 15 hands) aged 46 to 75 years (average, 59.7 years). The ratio of men to women was 1:11 in I-CTS and 1:1.1 in HD-CTS. There were 15 right hands and 13 left hands. Arms fitted with the intravenous shunt were involved in 17 hands and other arms were involved in 11 hands.

The surgical results were evaluated at follow-up according to Kelley's criteria (7). All patients of I-CTS were available for follow-up and follow-up duration ranged

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from 12 to 36 months (average, 18 months). Seventeen out of 28 hands of HD-CTS patients were followed-up. Follow-up duration ranged from 12 to 48 months (average, 26 months).

The specimens were procured during open surgery from the tenosynovium of the flexor tendon, the epineurium or surrounding nerve tissue, and the transverse carpal ligament. Sections of each specimen were stained with hematoxylin-eosin, Mallory-Azan, Masson trichrome and Congo red, and were examined by light and polarized light microscopy. All specimens that stained positively with Congo red underwent an additional test with the unlabeled antibody peroxidase-antiperoxidase (PAP) method and with anti-β_2 microglobulin antibody (Chemicon International, Inc., USA) on paraffin-embedded sections to confirm the identity of β_2-microglobulin.

The severity of each histological finding was divided into four groups according to occupied areas as follows: none, none was observed in the specimen; minimal, less than 20 %; moderate, 20 to 70 %; severe, over 70 %.

Results

Histological findings of the I-CTS group mainly consisted of edema and fibrosis or fibroblast proliferation in the tenosynovium and epineurium (Fig. 1). Edema and fibrosis were observed in more than 80 % of the specimens of the tenosynovium and epineurium in the I-CTS specimens. Vascular proliferation was relatively rare in all specimens. The proliferation of small vessels with thickening of the intima was sometimes also located in the tenosynovium and epineurium (Fig. 2). No signs of inflammation, such as round-cell infiltration, were found in any of these specimens.

There was no increase in the thickness of the transverse carpal ligament in I-CTS patients, nor were any histological changes apparent therein. Histological findings in the ligament were minimal, with the exception of degenerative changes (myxoid changes and hyalinization) (Fig. 3), which were observed in 70 % of the ligament specimens. These changes appeared to be secondary effects of the abnormal pressure exerted by the expansion of the volume of the synovium. The incidence of each finding appears in Table 1.

The histological findings of the HD-CTS group mainly consisted of amyloid deposition and macrophage infiltration (Fig. 4), which were found together in each tissue. Infiltration of macrophages and foreign-body giant cells, and granulation tissue proliferation were observed in the areas surrounding the amyloid deposits. The infiltration of macrophages and foreign-body giant cells increased in

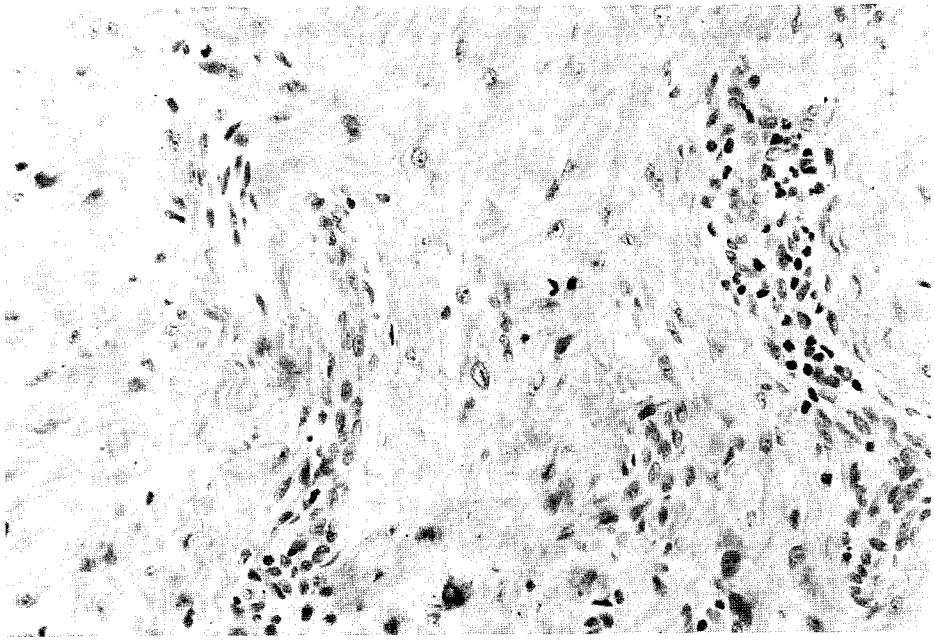

Fig. 1 Fibroblast proliferation in the tenosynovium of the idiopathic carpal tunnel syndrome (I-CTS) Group. (HE, × 200).

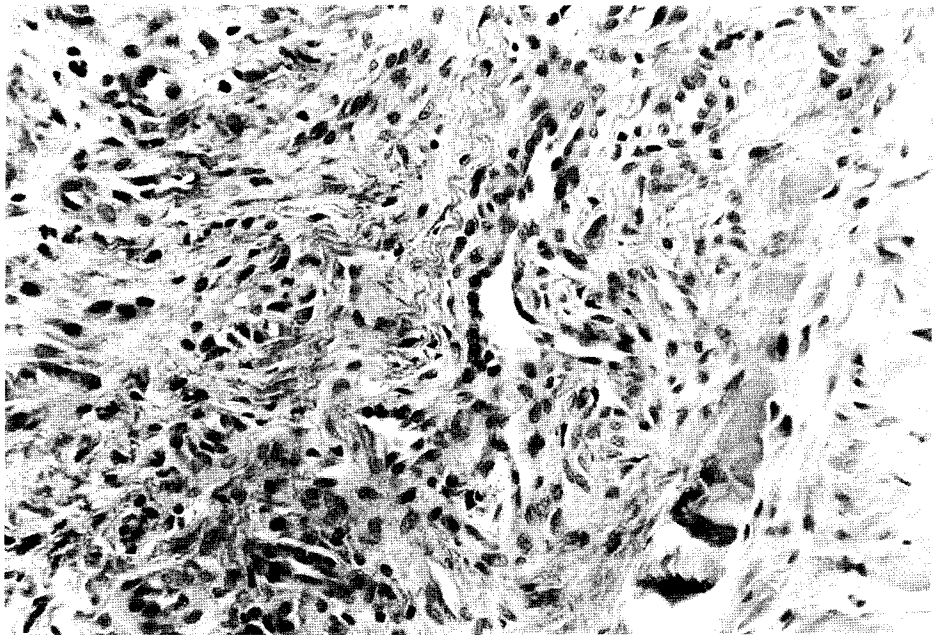

Fig. 2 Proliferation of small vessels with thickening of the intima in the tenosynovium of the I-CTS Group. (HE, × 200). I-CTS: See Fig. 1.

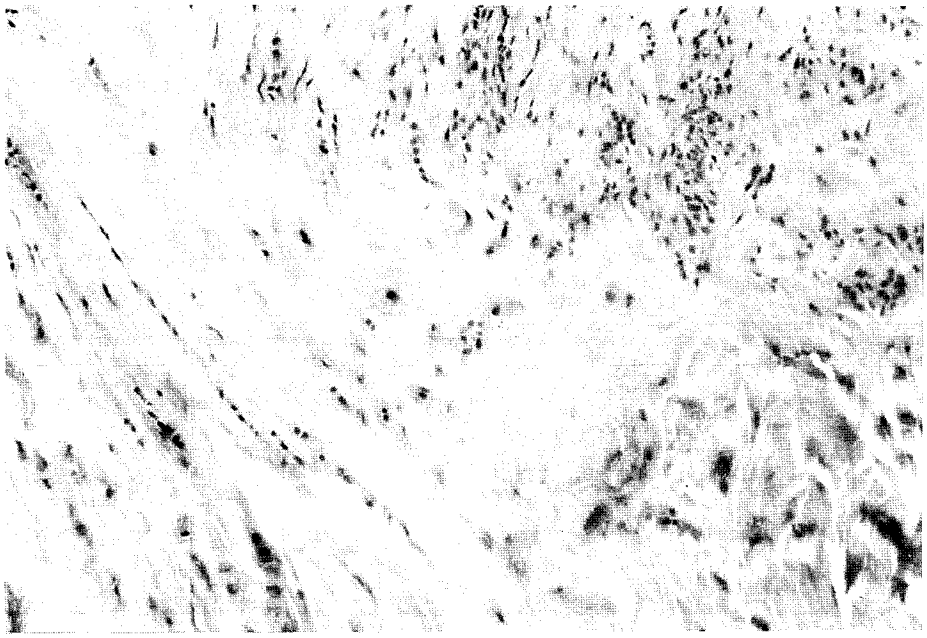

Fig. 3 Myxoid change and hyaline degeneration in the transverse carpal ligament of the I-CTS Group. (HE, × 200). I-CTS: See Fig. 1.

proportion to the amount of amyloid. The percentage of histological findings of the 28 specimens in each region is shown in Table 2. The deposition rates were over 90 % in the tenosynovium and the epineurium, and 76 % in the transverse carpal ligament. β_2-microglobulins were positively identified in the areas of amyloid deposition. Evi-

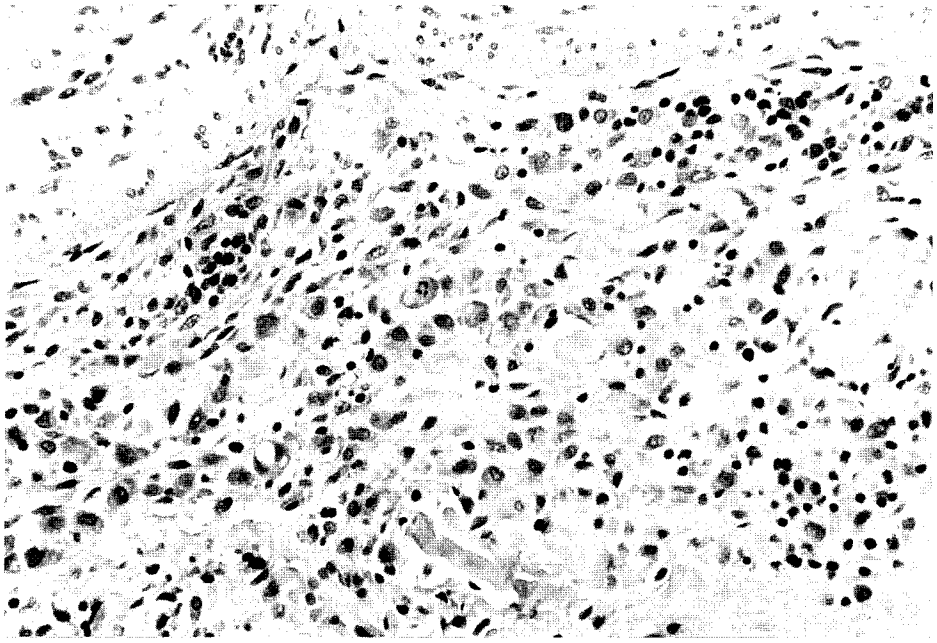

Fig. 4 Amyloid deposition and macrophage infiltration in the hemodialysis (HD)-CTS Group. (HE, × 200). CTS: See Fig. 1.

Table I Histological findings of idiopathic carpal tunnel syndrome (I-CTS)

Histological finding	Grade	Percentage of 40 specimens for each tissue		
		Tenosynovium	Epineurium	Ligament
Edema	(+)~(++)	83	80	0
	(−)~(±)	17	20	100
Fibrosis or fibroblast proliferation	(+)~(++)	80	83	40
	(−)~(±)	20	17	60
Vascular proliferation	(+)~(++)	21	7	8
	(−)~(±)	79	93	92
Myxoid change or hyalinzation	(+)~(++)	28	14	70
	(−)~(±)	72	86	30

(−) None; (±) Minimal; (+) Moderate; (++) Severe.

dence of inflammation in the hemodialysis group included macrophage infiltration in 50 % of the tenosynoviums, in 33 % of the epineuriums and in 75 % of the transverse carpal ligament specimens.

Amyloid deposits, positively identified as β_2-microglobulins, which appeared in all patients in HD-CTS, were not observed in any specimens of I-CTS. Macrophage infiltration was none or minimal. In contrast to the I-CTS specimens, in the HD-CTS specimens, vascular proliferation, myxoid change and hyalinization were minimal.

The amyloid deposits were easily identified because the Congo red staining turned a distinctive greenish-orange under polarized light (Fig. 5). The PAP test results confirmed that the amyloid deposits were β_2-microglobulin. The amyloid deposits in specimens of this group were observed in the tenosynovium, in the tissues surrounding the nerves and in the transverse carpal ligament.

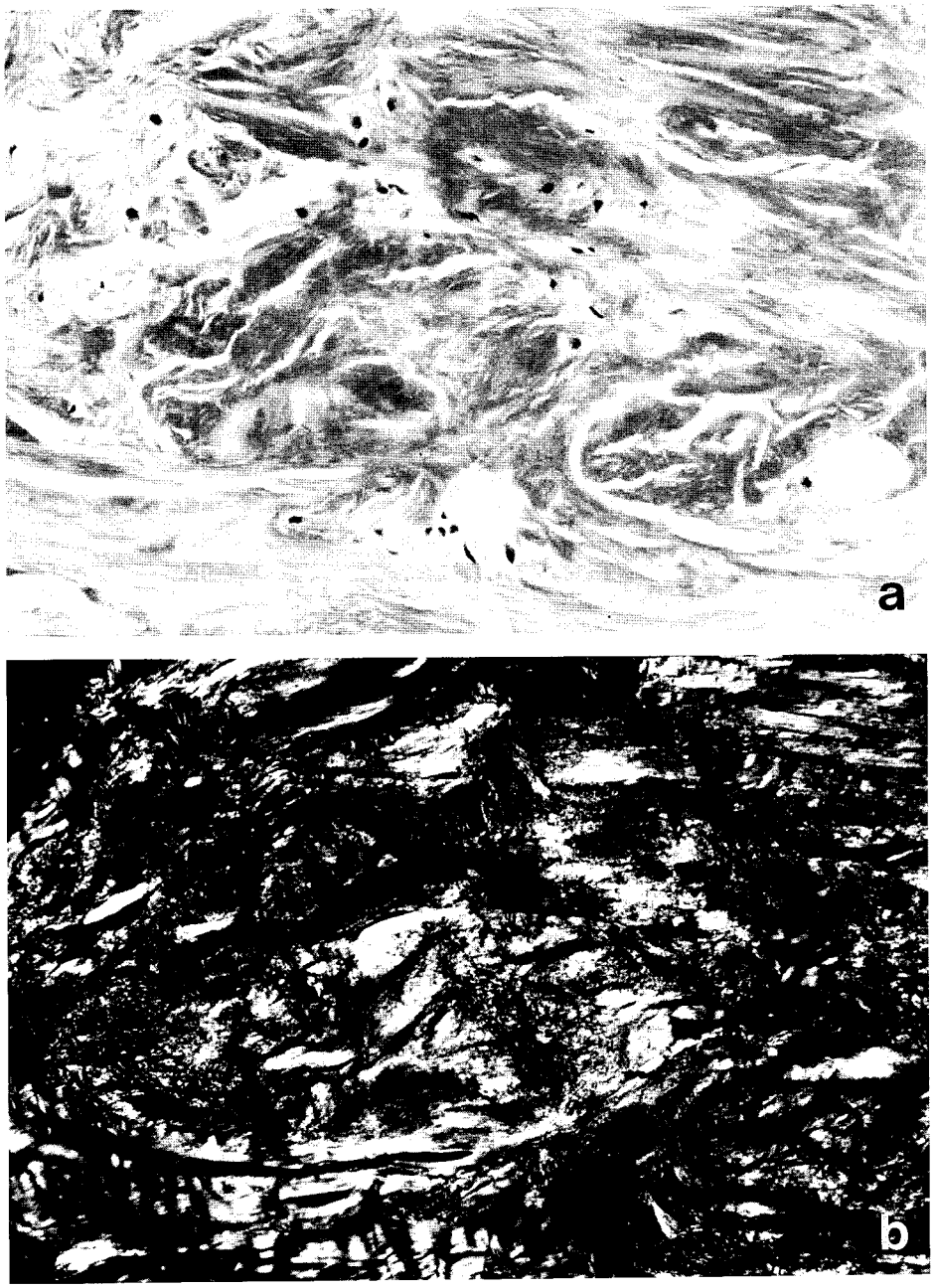

Fig. 5 Amyloid deposits. **a**) HE, × 200. **b**) Congo red, × 200.

The amyloid deposits ranged from particles to small nodules arranged parallel to the collagen fibers.

All patients experienced resolution of the pain and/or reduced numbness after surgery. Of 40 hands with I-CTS, 21 (53 %) were excellent, 12 (30 %) good and 7 (17 %) fair. Of 17 hands with HD-CTS, 8 (47 %) were excellent, 4 (24 %) good, and 5 (29 %) fair.

The relationship between histological findings, preoperative grade and surgical results in both I-CTS and HD-CTS is shown in Tables 3 and 4. Fibrosis of epineurium for I-CTS and amyloid deposition in tenosynovium for HD-CTS were chosen as histological

Table 2 Histological findings of hemodialysis related (HD)-CTS

Histological finding	Grade	Percentage of 28 specimens for each tissue		
		Tenosynovium	Epineurium	Ligament
Amyloid deposition	(+)~(++)	93	90	76
	(−)~(±)	7	10	24
β2-microglobulin	(+)~(++)	93	90	76
	(−)~(±)	7	10	24
Macrophage infiltration	(+)~(++)	50	33	75
	(−)~(±)	50	67	25
Fibrosis or fibroblast proliferation	(+)~(++)	10	33	38
	(−)~(±)	90	67	62

(−) None; (±) Minimal; (+) Moderate; (++) Severe. CTS: See Table I.

Table 3 Comparison of histological findings and clinical history in I-CTS patients

Fibrosis of epineurium	Preoperative grade (n = 40)			Surgical result (n = 40)			
	I	II	III	Excellent	Good	Fair	Poor
(+)~(++)	10	16	7	15	12	6	0
(−)~(±)	3	3	1	6	0	1	0

(−) None; (±) Minimal; (+) Moderate; (++) Severe. I-CTS: See Table I.

Table 4 Comparison of histological findings and clinical history in HD-CTS patients

Amyloid deposition in tenosynovium	Preoperative grade (n = 17)			Surgical result (n = 17)			
	I	II	III	Excellent	Good	Fair	Poor
(±)~(++)	6	4	4	7	2	5	0
(−)~(±)	1	2	0	1	2	0	0

(−) None; (±) Minimal; (+) Moderate; (++) Severe. HD-CTS: See Tables I, 2.

findings which seemed to be responsible for the clinical manifestations. The fibrosis of epineurium in preoperative Grade III group of I-CTS patients was moderate to severe in all but one case. The surgical results in the none and minimal fibrosis groups were excellent in all but one case. The surgical results in the none and minimal amyloid deposition groups of HD-CTS were also excellent or good.

Discussion

The onset mechanism of I-CTS has been attributed to non-specific findings, such as edema and fibrosis in the flexor tenosynovium induced by internal factors, such as hormones, and to enhancement of external factors, including friction generated by over-use (8). This results in a relative narrowing of the carpal tunnel caused by the edema and fibrosis of the tenosynovium and the epineur-

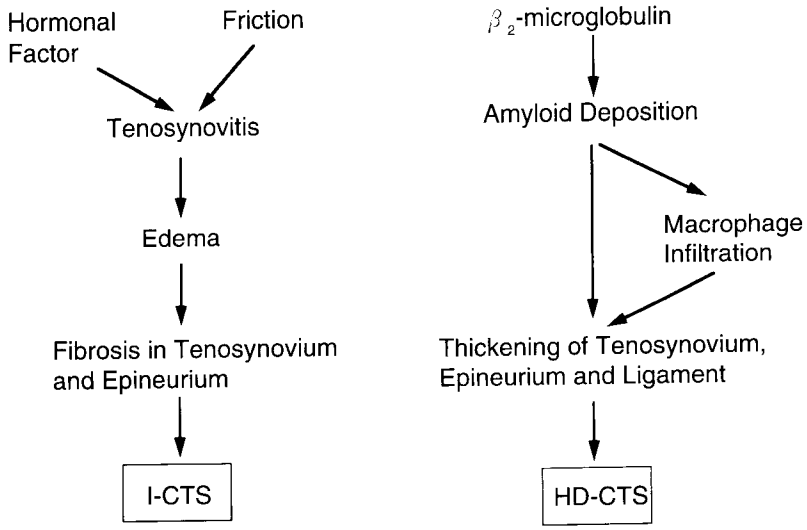

Fig. 6 Flow chart of the onset Mechanisms of CTS. I-CTS: See Fig. 1, HD-CTS: See Fig. 4.

ium which gives rise to the typical complaints of CTS. Schuind *et al.* (3) described a degeneration of the connective tissue under repeated mechanical stresses. However, these findings, which we also observed, seemed to be a secondary effect derived from increased pressure in the carpal tunnel. Increased pressure caused by thickening of the tenosynovium initiates the vicious destructive cycle in I-CTS, not the initial mechanical stress. Edema followed by fibrosis also plays a major role in the pathogenesis related to hormonal changes in premenopausal or pregnant women (3).

The onset mechanism of HD-CTS has not been established. Four theories have been reported, as follows: a) the vulnerability of the median nerve caused by uremic toxin (9); b) increased extracellular fluid (10), c) change of blood flow because of a shunt (11) and d) increase of carpal tunnel pressure caused by amyloid deposition (12–14). The deposition of β_2-microglobulin amyloid (15, 16) in any of those areas, followed by reactive infiltration of macrophages and foreign-body giant cells, proliferation of synovial tissue and granulation tissue formation, can produce the same effect.

The main histopathological findings suggest that CTS lesions are caused by nerve compression induced by fibrous hypertrophy of the tenosynovium and epineurium in the idiopathic group (3) and by inflammatory reaction to the amyloid deposition in the tenosynovium, epineurium and ligament in the hemodialysis group (Fig. 6).

The etiology of HD-CTS seems to involve increased carpal tunnel pressure caused by the relative narrowing of the carpal tunnel because of amyloid deposition. Amyloid deposition occurs easily in high-stress areas, such as the bursa or tenosynovium. Then, a vicious cycle may occur, in which mechanical stress induces amyloid deposition and amyloid deposition in turn increases the carpal tunnel pressure, thereby causing greater mechanical stress. The relation between HD-CTS and cystic radiolucency, which reflects the degree of synovitis, has been reported (17). We believe that the increase of internal pressure in the closed space of the carpal tunnel acts to destroy the surrounding bony structure.

Although the pathogeneses varied, the end result in each case was nerve compression. Surgery is effective for HD-CTS patients, even in the early stages of the syndrome. Furthermore, early carpal tunnel release is recommended for HD-CTS patients. If it is not done, a more radical operative procedure becomes necessary (18). Fortunately, hemodialysis patients generally notice intermittent pain while they are still in the early stages, and the surgical outcome and prognosis are often excellent. Patients with I-CTS tend to notice symptoms at later stages, and consequently, their periods of recovery may be relatively longer. Surgical release must also be selected for I-CTS cases where conservative treatment is ineffective or inappropriate.

The main histological findings suggest that in the

I-CTS cases, compression of the nerve was caused by edema and fibrosis in the tenosynovium and in the epineurium. The main compression factor in the patients with HD-CTS was also a space-occupying lesion induced by amyloid deposition that appeared mainly in the tenosynovium and the epineurium rather than in the transverse carpal ligament. The findings for the two groups revealed distinctively different pathogeneses but similar onset mechanisms of CTS.

Surgical release is recommended at the earliest possible stage in long-term hemodialysis cases, and in idiopathic cases where conservative treatment has been unsuccessful or contraindicated. Surgeons need not hesitate to surgically treat HD-CTS. Surgical release can provide relief from pain within hours in the early stages of the syndrome. This is an important consideration in patients for whom relief from pain and quality of life are paramount.

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