

ORIGINAL**Radiographic changes of cervical destructive spondyloarthropathy in long-term hemodialysis patients : A 9-year longitudinal observational study**

Akihiro Nagamachi¹⁾, Mitsuhiro Takahashi²⁾, Noriaki Mima²⁾, Keisuke Adachi²⁾, Kazumasa Inoue²⁾, Subash C. Jha¹⁾, Akihiro Nitta¹⁾, Masatoshi Morimoto¹⁾, Tomoya Takasago¹⁾, Toshiyuki Iwame¹⁾, Keizo Wada¹⁾, Fumitake Tezuka¹⁾, Kazuta Yamashita¹⁾, Humio Hayashi¹⁾, Ryo Miyagi¹⁾, Toshihiko Nishisyo¹⁾, Ichiro Tonogai¹⁾, Tomohiro Goto¹⁾, Yoichiro Takata¹⁾, Toshinori Sakai¹⁾, Kosaku Higashino¹⁾, Takashi Chikawa³⁾, and Koichi Sairyō¹⁾

¹⁾Department of Orthopedic Surgery, Tokushima University, Tokushima, Japan, ²⁾Department of Orthopedic Surgery, Mitoyo General Hospital, Kanonji, Japan, ³⁾Department of Orthopedic Surgery, Tokushima Municipal Hospital, Tokushima, Japan

Abstract : Analyses of radiographic changes and clinical symptom of destructive spondyloarthropathy (DSA) on consecutive 42 patients managed with long-term hemodialysis were performed to elucidate radiographic changes of DSA and the factors that influence to the destructive changes. Patients underwent plain radiographs of the cervical spine with 9 years interval. Grading of radiological feature from lateral view was classified into grade 0 to grade 3. Clinical symptom was evaluated using modified Japanese Orthopaedic Association scoring system for cervical myelopathy (mJOA score). Destructive changes were observed in 3 patients at the first examination, and those were observed in 15 patients 9 years after the first examination. There is no statistically significant difference between the duration of hemodialysis and the grade. The mean age at the onset of hemodialysis, however, was significantly higher in patients of grade 2 and 3 than those of grade 1. Older patients with long-term hemodialysis had destructive changes. Destructive changes commonly observed in lower cervical spine. The average numbers of the involved disc level were 1.6 in grade 2 and 1.0 in grade 3. Clinical symptoms were varied in each grade and there was no statistically significant difference in total mJOA score among these grades. *J. Med. Invest.* 64 : 68-73, February, 2017

Keywords : destructive spondyloarthropathy, hemodialysis, radiological analysis, clinical symptom

INTRODUCTION

Advancement of techniques and instruments of hemodialysis brings improvement of the survival rate and opportunity to return to the social life for the chronic renal failure patients. On the other hand, the number of disabled patients due to bone and joint diseases in association with hemodialysis expands as the number of hemodialysis patients increases and their lifespan prolongs. The number of patients underwent hemodialysis was 215 in 1968 and 320,448 in 2014 (1). Destructive spondyloarthropathy (DSA) is one of the most significant spinal disorders associate with long-term hemodialysis. Since Kuntz *et al.* first described DSA in 1984 (2), many authors have reported on its pathology (3, 4), causative factors (5-11) and management (12-18). Patients with DSA are suffering from sever neck pain and sometimes have neurologic deficit. Operative treatment is sometimes indicated for these patients. Although it is important to know natural course of DSA for the treatment of the patients, there are few previous longitudinal studies (10, 19). The purpose of this longitudinal study is to elucidate radiological changes of the cervical spine during 9 years and clinical symptom of DSA in long term-hemodialysis.

PATIENT AND METHODS

Forty-two patients out of 94 patients being managed with hemodialysis at Mitoyo General Hospital in 1998 have had undergone plain radiography in 1989. These 42 patients participated in this study. There were 24 male and 18 female ranged in age from 38 to 80 years old (mean, 58 years old). Duration of hemodialysis ranged from 9 to 25 years (mean, 15.3 years) at the first radiological examination. Distribution of age and duration of hemodialysis were not statistically significant difference between male and female. Nephropathy was caused by glomerulonephritis in 38 patients and by diabetes mellitus in 4 patients. All patients underwent anteroposterior and lateral views of plain radiography of the cervical spine in 1989 for the first examination. Nine years after the initial radiography, all patients underwent follow-up plain radiography of the cervical spine for the second examination in 1998. Radiological findings of the lateral view were graded as follows. Normal findings without any disc space narrowing, erosive changes and subluxation was defined as grade 0. Erosive changes in anterior rim of the vertebrae and endplate without remarkable disc space narrowing were defined as grade 1. Remarkable disc space narrowing with minimal osteophyte formation was defined as grade 2. Spinal fusion and/or subluxation of the vertebrae was defined as grade 3 (Fig. 1). The grade of the finding was determined in consultation by two orthopedic surgeons. All patients were graded according to their findings at the first and the second examination. The relationships between the duration of hemodialysis and the grade and between the age at the onset of hemodialysis and the grade were evaluated. Also radiological changes at each disc level from C2-3 to C6-7 were observed at the first and the second examination. Clinical symptom

Received for publication August 8, 2016 ; accepted November 11, 2016.

Address correspondence and reprint requests to Akihiro Nagamachi, Department of Orthopedic Surgery, Tokushima University 3-18-15, Kuramoto, Tokushima, 770-8503, Japan and Fax : +81-88-633-0178.

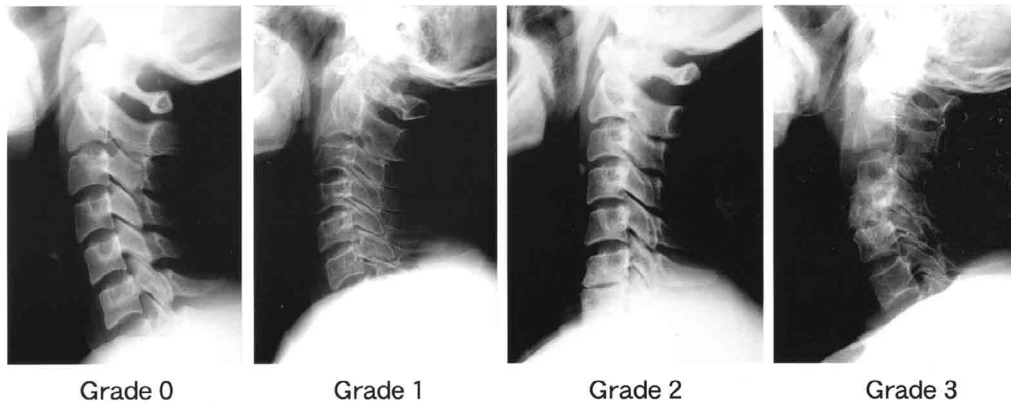


Figure 1. Radiographic grading of cervical destruction on the lateral view.

Grade 0 : normal ; grade 1 : erosive changes in the anterior rim of the vertebrae and endplate ; grade 2 : disc space narrowing with minimal osteophyte formation ; grade 3 : spinal fusion and/or subluxation of the vertebrae.

at the second examination was evaluated by modified Japanese Orthopaedic Association scoring system for cervical myelopathy (Table 1). Statistical analysis was performed using unpaired student-*t* test, Fisher's exact test, one way ANOVA and Fisher's PLSD for post hoc test. For all statistical analyses, the $p < 0.05$ level of significance was used.

RESULTS

At the first examination, 9 patients (21.4%) were classified into grade 0, 30 patients (71.4%) were classified into grade 1, 3 patients (7.1%) were classified into grade 2 and no patient was classified into grade 3. Nine years after the first examination, 1 patient (2.4%) was classified into grade 0, 26 patients (61.9%) were classified into grade 1, 7 patients (16.7%) were classified into grade 2 and 8 patients (19.0%) were classified into grade 3. Patient classified into grade 2 and grade 3 were observed in 7.1% of the patients at the first examination, conversely those were observed 35.7% at the second examination (Fig. 2). The mean duration of hemodialysis of patients with grade 1, grade 2 and grade 3 was 15.5 ± 4.2 years, 14.9 ± 4.9 years and 15.2 ± 4.0 years, respectively with no statistically significant difference. On the other hand, mean age at the onset of hemodialysis of patients with grade 1, grade 2 and grade 3 was 39.2 ± 9.6 years, 48.2 ± 11.9 years and 49.6 ± 10.5 years, respectively. Mean age at the onset of hemodialysis of grade 2 and grade 3 were significantly older than that of grade 1 (Fig. 3)

A decrease in the number of patients of grade 0 and an increase of grade 1 were observed in all disc levels during nine years. Radiological changes of grade 2 and grade 3 significantly increased in C5-6 and C6-7 disc levels (Fig. 4). The average numbers of the involved disc level were 1.6 in grade 2 and 1.0 in grade 3 at the second examination.

Of 8 patients in grade 3, 2 patients had grade 2 changes in an adjacent disc level.

Clinical symptom was varied in each grade. There was no statistically significant difference among all grade in total mJOA score, however, there was statistically significant difference between grade 1 and grade 3 in shoulder and elbow function scores (Table 2).

A CASE PRESENTATION

Figure 5 shows radiological changes of a 65 years old male patient who has been managed with hemodialysis during 8 years at

the first examination. He was classified into grade 1 at the first examination and was classified into grade 3 at the second examination. At the first examination, radiological changes of grade 1 were observed in the levels of C3-4, C4-5 and C5-6. At the second examination, duration of hemodialysis was 17 years and the radiological changes of grade 3 were observed in the levels of C3-4 and C4-5. Total mJOA score was 11 point at the second examination (Fig. 5).

DISCUSSION

Since Kuntz *et al.* first described DSA as a new syndrome associated with long-term hemodialysis (2), many possible cause of DSA have been considered. Recently, most authors consider that the main cause of DSA is deposition of $\beta 2$ -microglobulin (3, 4, 8, 20, 21). In chronic renal failure and long-term hemodialysis patients, $\beta 2$ -microglobulin deposit in articular, periarticular and perineural tissues because $\beta 2$ -microglobulin could not be filtered by the kidney and the column. Sebert *et al.* demonstrated that deposition of amyloid resulting from $\beta 2$ -microglobulin in the vertebral disc of patient with DSA (11). Miyata *et al.* attested $\beta 2$ -microglobulin modified with advanced glycation end products (AGEs) is the major component of hemodialysis-associated amyloidosis (21). AGEs induce transendothelial human monocyte chemotaxis and production of TNF alpha and IL-1 β . Activation of osteoclast or chondroclast by TNF alpha and IL-1 β promotes bone absorption, causing destructive changes of the cervical spine (22).

Maruyama *et al.* described that patient's age at the onset of hemodialysis was an associate risk factor for DSA (8). In the present study, we also found that duration of hemodialysis did not correlate to progress of destructive changes. Conversely, patient's age at the onset of hemodialysis correlated to progress of destructive changes. Older patients with long-term hemodialysis had destructive changes. Although the cause of DSA is thought to be deposition of AGEs $\beta 2$ -microglobulin in the disc, ligament and vertebrae, it is not enough to explain the pathogenesis of DSA. If AGEs $\beta 2$ -microglobulin deposition is the main cause of DSA, destructive changes should have occurred in younger patients. Therefore, aging is thought to be one of the most important factors of DSA.

DSA developed commonly in the lower cervical spine of which range of motion was larger. These destructive changes were limited in one or sometimes two disc levels. It was thought that once the destructive changes had occurred, axial and shearing loads were concentrated to the involved level and destruction progressed

Table 1. Modified Japanese Orthopaedic Association scoring system for cervical myelopathy

Category
A. MOTOR FUNCTION :
I. Fingers
0=Unable to feed oneself with any tableware including chopsticks, a spoon or fork and/or unable to fasten buttons of any size
1=Can manage to feed oneself with a spoon and/or a fork but not with chopsticks
2=Either chopstick-feeding or writing is possible but not partial, and/or large buttons can be fastened
3=Either chopstick-feeding or writing is clumsy but partial, and/or cuff buttons can be fastened
4=Normal
II. Shoulder and Elbow
Evaluated by MMT score of the deltoid or biceps muscle, which is weaker
-2=MMT 2 or below
-1=MMT 3
-0.5=MMT 4
0=MMT 5
III. Lower Extremity
0=Unable to stand up and walk by any means
0.5=Able to stand up but unable to walk
1=Unable to walk without a cane or other support on a level
1.5=Able to walk without a support but needs support on stairs
2=Walks independently on a level but needs support on stairs
2.5=Walks independently when going upstairs, but needs support when going downstairs
3=Capable of fast walking but clumsily
4=Normal
B. SENSORY FUNCTION
I. Upper Extremity
0=Complete loss of touch and pain sensation
0.5=50% or below of normal sensation and/or severe pain or numbness
1=Over 60% of normal sensation and/or moderate pain or numbness
1.5=Subjective numbness of a slight degree without any objective sensory deficit
2=Normal
II. Trunk
0=Complete loss of touch and pain sensation
0.5=50% or below of normal sensation and/or severe pain or numbness
1=Over 60% of normal sensation and/or moderate pain or numbness
1.5=Subjective numbness of a slight degree without any objective sensory deficit
2=Normal
III. Lower Extremity
0=Complete loss of touch and pain sensation
0.5=50% or below of normal sensation and/or severe pain or numbness
1=Over 60% of normal sensation and/or moderate pain or numbness
1.5=Subjective numbness of a slight degree without any objective sensory deficit
2=Normal
C. NECK AND SHOULDER PAIN
0=Frequent or continuous severe pain
1=Frequent mild or occasional severe pain
2=Occasional mild pain
3=None
Total for normal patient 17

in limited disc levels. The mechanical stress to the spine is associated with the pathogenesis of DSA. Of 8 patients with grade 3, 2 patients had grade 2 changes in an adjacent disc level in this study. This fact is important to plan the extent of spinal fusion level. Sudo *et al.* performed reconstructive surgery for patients with significant spinal instability and reported that progressive destructive changes causing significant instability in the mobile segments

adjacent to the previous fusion site were observed in four patients (40%) who underwent circumferential fusion (23). It is important to extent fusion if adjacent disc level had grade 1 or grade 2 changes.

In the present study, mJOA scores were inconsistent and low in all grades and there was no statistically significant correlation between radiological findings and clinical symptom except shoulder

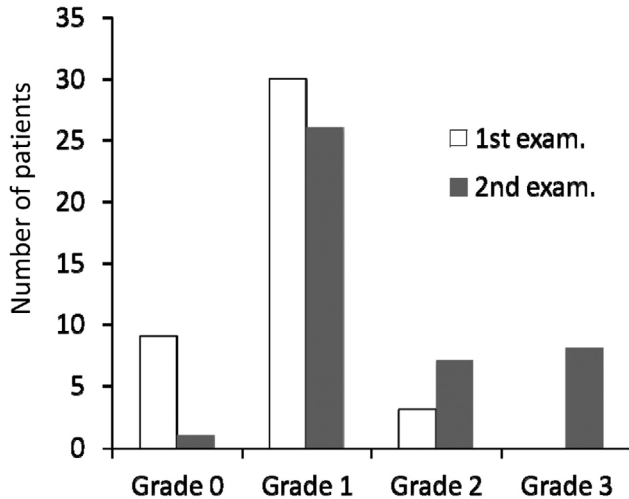


Figure 2. Number of patients with each grade of radiographic changes at the first and second examinations. Grades 2 and 3 were observed in 7.1% of the patients at the first examination and in 35.7% at the second examination.

and elbow functions. Two of 8 patients of grade 3 complained mild pain on their neck, while 4 of 27 patients in grade 1 complained continuous severe pain on their neck. Many patients had numbness in their limbs because of peripheral neuropathy caused by amyloid deposition including carpal tunnel syndrome and tarsal tunnel syndrome. Thus, clinical symptom did not correlate with the radiological findings. Even though total mJOA scores were low, no patient required surgery in this series. Patients with DSA occasionally complain severe neck pain and sometimes have radiculomyelopathy. Surgery would be performed when rapid neurological deterioration (12) is observed. Patients with DSA have many other complications, including cardiopulmonary disease, immunosuppression due to diabetes mellitus and sometimes hepatocellular carcinoma resulting from hepatitis C. Nakamura *et al.* investigated the survival rate of the patients with DSA and concluded

that the survival rate was 37.4% over 10 years from the onset of hemodialysis and 0% over 20 years (24). Large amount of bleeding, surgical site infection and osteopenia are some of the major problems at surgery. Kumar *et al.* demonstrated that successful cervical spine fusion could relieve pain and neurologic deficits in selected patients (16). However, 2 of the 11 patients who underwent surgery died during perioperative period. Itoh *et al.* performed surgery for 17 patients with DSA and 1 patient died during the operation and 2 patients died perioperative period (15). Naito *et al.* studied the outcome of 9 patients who had surgery for DSA and concluded that 5 patients had good, 2 patients had fair and 1 patient had poor results (18). They also reported that 1 patient died 46 days after the surgery due to postoperative meningitis. Because of such high mortality, patient selection based on their disability, general condition and prognosis is important.

CONCLUSION

During 9 years, number of patients with destructive changes increased from 3 (7.1%) to 15 (35.7%). In the present study, we found that duration of hemodialysis did not correlate to progress of destructive changes. Conversely, patient's age at the onset of hemodialysis correlated to progress of destructive changes. Destructive changes progressed in older patients with long-term hemodialysis. Destructive changes progressed in the lower cervical spine and occurred in limited number of the disc level. Mean mJOA score was low, however, there was no patient required surgery in this series. There was no statistical correlation between radiological findings and mJOA score.

CONFLICT OF INTEREST

There is nothing to declare of conflict of interest for this work.

ACKNOWLEDGEMENTS

The authors thank to Mamoru Hirohata, M.D., Toru Endo, M.D.,

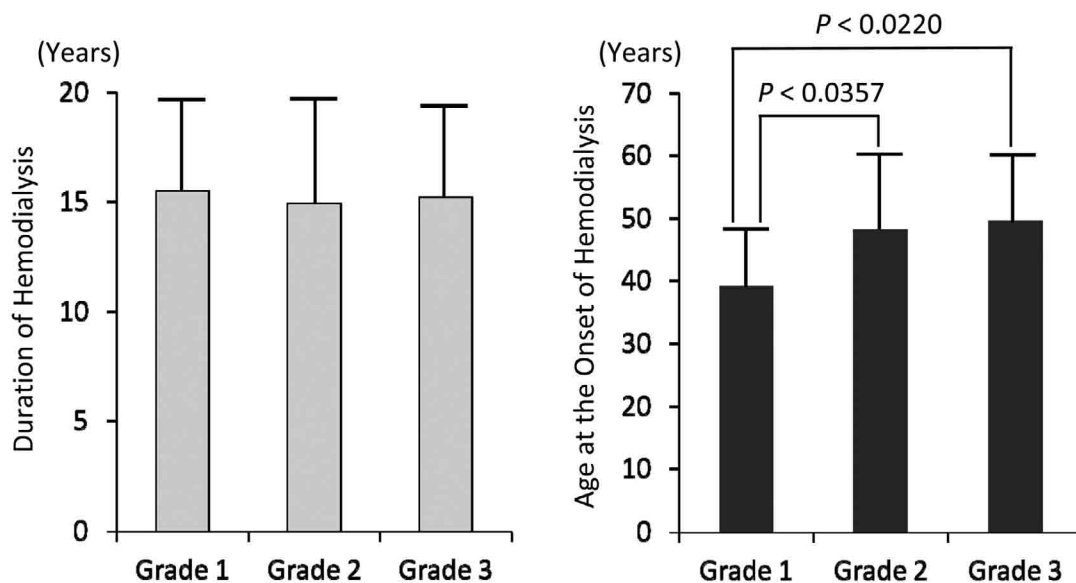


Figure 3. Grade versus duration of hemodialysis and age at initiation of hemodialysis. Mean age at initiation of hemodialysis was significantly higher in patients with grades 2 or 3 than in those with grade 1.

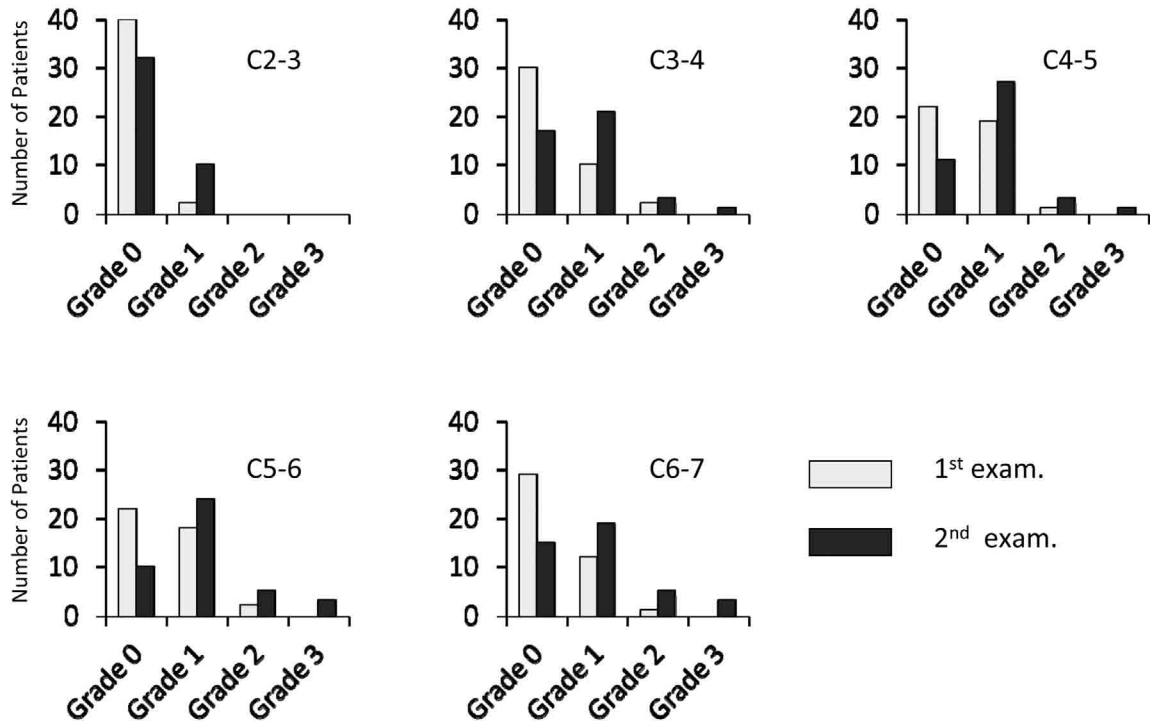


Figure 4. Radiographic changes in each disc level. Radiographic changes of grades 2 and 3 were most commonly observed in the lower cervical spine.

Table 2. Modified Japanese Orthopaedic Association scores by grade of radiographic changes at the second examination

	Motor Function			Sensory Function			Neck Pain	Total
	Fingers (4)	Shoulder and Elbow (0)	Lower Extremity (4)	Upper Extremity (2)	Trunk (2)	Lower Extremity (2)	(4)	(17)
Grade 1	3.3±0.8	-0.2±0.5	2.7±1.1	1.8±0.5	1.8±0.3	1.7±0.4	2.1±0.7	12.7±2.9
Grade 2	3.1±1.4	-2.5±0.5	2.4±1.3	1.6±0.7	1.7±0.6	1.6±0.6	2.0±0.8	11.9±4.7
Grade 3	3.6±0.5	-0.7±1.0	2.1±1.0	1.6±0.8	1.6±0.6	1.5±0.6	2.1±0.7	11.4±3.1

(Mean±SD, *P< 0.05)

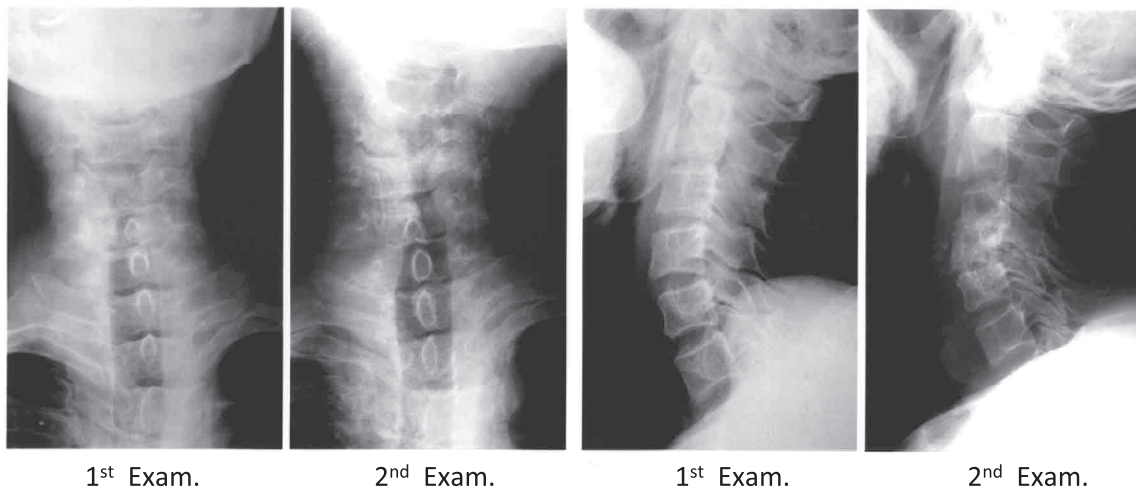


Figure 5. Radiographs showing the radiographic changes in a 65-year-old man who had been on hemodialysis for 17 years. At the second examination, grade 3 radiographic changes were observed in the C3-4 and C4-5 levels.

Kenji Akiyama, M.D. and Tsutomu Ishizu, M.D. for their work in the coordination of this study.

REFERENCES

1. The Japanese Society for Dialysis Therapy. The basic statistic of hemodialysis patients in Japan (in Japanese) : <http://docs.jsdt.or.jp/overview/pdf2015/p003.pdf>
2. Kuntz D, Naveau B, Bardin T, Druke T, Treves R, Dryll A : Destructive spondyloarthropathy in hemodialysed patients. A new syndrome. *Arthritis Rheum* 27 : 369-375, 1984
3. Bardin T, Zingraff J, Shirahama T : Hemodialysis-associated amyloidosis and beta-2 microglobulin-Clinical and immunohistochemical study . *Am J Med* 83 : 419-424, 1987
4. Moriniere Ph, Marie A, Esper NE : Destructive spondyloarthropathy with β 2-microglobulin amyloid deposits in a uremic patient before chronic hemodialysis. *Nephron* 59 : 654 - 657, 1991
5. Alcalay M, Goupy MC, Azais I, Bontoux D : Hemodialysis is not essential for the development of destructive spondyloarthropathy in patients with chronic renal failure. *Arthritis Rheum* 30 : 1182-1186, 1987
6. Bindi P, Lavaud S, Bernieh B, Toupance O, Chanard J : Early and late occurrence of destructive spondyloarthropathy in hemodialysed patients. *Nephrol Dial Transplant* 5 : 199-203, 1990
7. Kaplan P, Rensnick D, Murphey M, Heck L, Phalen J, Egan D, Rutsky E : Destructive noninfectious spondyloarthropathy in hemodialysis patients : A report of four cases. *Radiology* 162 : 241-244, 1987
8. Maruyama H, Gejyo F, Arakawa M : Clinical studies of destructive spondyloarthropathy in long-term hemodialysis patients. *Nephron* 61 : 37-44, 1992
9. McCarthy J, Dahlberg PJ, Krie gshauser JS : Erosive spondyloarthropathy in long-term dialysis patients : Relationship to severe hyperparathyroidism. *Mayo Clin Proc* 63 : 446-452, 1988
10. Orzincolo C, Bedani PL, Scutellari PN, Cardona P, Trotta F, Gilli P : Destructive spondyloarthropathy and radiographic follow-up in hemodialysis patients. *Skeletal Radio* 19 : 483-487, 1990
11. Sebert JL, Fardellone P, Marie A : Destructive spondyloarthropathy in hemodialysed patients : Possible role of amyloidosis. *Arthritis Rheum* 29 : 301-302, 1986
12. Davidson GS, Montanera WJ, Fleming JFR, Gentili F : Amyloid destructive spondyloarthropathy causing cord compression : Related to chronic renal failure and dialysis. *Neurosurgery* 33 : 519-522, 1993
13. Deforges-Lasseur C, Combe C, Cernier A, Vital JM, Aparico M : Destructive spondyloarthropathy presenting with progressive paraplegia in a dialysis patient. Recovery after surgical spinal cord decompression and parathyroidectomy. *Nephrol Dial Transplant* 8 : 180-184, 1993
14. Digenis GE, Davidson G, Dombros NV, Katz A, Bookman A, Oreopoulos DG : Destructive spondyloarthropathy in a patient on continuous ambulatory peritoneal dialysis for 13 years. *Pert Dial Int* 13 : 228-231, 1993
15. Ito M, Abumi K, Kaneda K, Takeda N, Satoh S, Takebayashi T : Surgical treatment of destructive spondyloarthropathy associated with long term hemodialysis (in Japanese). *Spine & Spinal Cord* 10 : 1079-1085, 1997
16. Kumar A, Leventhal MR, Freedman EL, Coburn J, Delamarter R : Destructive spondyloarthropathy of the cervical spine in patients with chronic renal failure. *Spine* 22 : 573-578, 1997
17. Mikawa Y, Yamaoka T, Watanabe R : Compression of the spinal cord due to destructive spondyloarthropathy of the atlantoaxial joints. *J Bone Joint Surg [Am]* 78-A : 1911-1914, 1996
18. Naito M, Ogawa K, Nakamoto M, Goya T, Sugioka Y : Destructive spondyloarthrppathy during long-term hemodialysis. *J Bone Joint Surg [Br]* 74-B : 686-690, 1992
19. Naidich JB, Mossey RT, McHeffey-Atkinson B : Spondyloarthropathy from long-term hemodialysis. *Radiology* 167 : 761-764, 1988
20. Kroner G, Stabler A, Seiderer M, Moran JE, Gurland HJ : β 2 microglobulin-related amyloidosis causing atlantoaxial spondyloarthropathy with spinal-cord compression in haemodialysis patients : Detection by MRI. *Nephrol Dial Transplant Suppl* 2 : 91-95, 1991
21. Miyata T, Oda O, Inagi R : β 2-microglobulin modified with advanced glycogen end products is a major component of hemodialysis-associated amyloidosis. *J Clin Invest* 92 : 1243-1251, 1993
22. Vlassara H, Brownlee M, Manogue KR, Dinarello CA, Pasagian A : Cachectin/TNF and IL-1 induced by glucose-modified proteins : role in normal tissue remodeling. *Science* 240 : 1546-1548, 1988
23. Sudo H, Ito M, Abumi K, Kotani Y, Takeuchi T, Yasui K, Minami A : Long-term follow up of surgical outcomes in patients with cervical disorders undergoing hemodialysis. *J Neurosurg Spine* 5 : 313-319, 2006
24. Nakamura M, Taketomi E, Matsunaga S : Long term follow up of destructive spondyloarthropathy in hemodialysed patients (in Japanese). *J Jpn Resea Soci Spine* 25 : 70-72, 1999