Calcium pyrophosphate dihydrate deposits in the cervical ligamenta flava causing myeloradiculopathy

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Three cases of cervical myeloradiculopathy associated with multiple calcified nodules containing identified calcium pyrophosphate dihydrate (CPPD) crystals in the ligamenta flava are described, with a comprehensive review of the 12 cases of this entity reported to date. The disease is characterized by: 1) oval or triangular areas of radiodensity in the posterior aspect of the cervical canal as seen in the lateral x-ray films and laminograms; 2) hemispherical areas of high density located almost symmetrically in the paramedial portion of the posterior spinal canal on computerized tomography scans; and 3) CPPD crystals in the nodules. It occurs independently or in association with cervical spondylosis or ossification of the posterior longitudinal ligament.

KEY WORDS - spinal cord compression - spinal nerve root - ligamentum flavum - calcification - chondrocalcinosis - calcium pyrophosphate dihydrate crystal deposits - myelopathy - radiculopathy

In 1962, McCarty and co-workers first discovered microcrystals of calcium pyrophosphate dihydrate (CPPD) in the leukocytes of fluid from inflamed joints of patients with painful arthropathy. It was called "articular chondrocalcinosis" by Zitnian and Sitaj. Since then, there have been several reports of "CPPD deposit disease" with characteristic articular linear radiodensities with or without associated diseases such as diabetes mellitus, hyperparathyroidism, classical gout, osteoarthritis, hemochromatosis, chronic renal disease, and neuropathic joints. Careful radiological and crystallographic studies of the menisci from cadavers have revealed three different microcrystalline species: 1) CPPD-Ca₂P₂O₇-2H₂O; 2) calcium orthophosphate CaHPO₄-2H₂O; and 3) hydroxyapatite-Ca₁₀(PO₄)₆(OH)₂⁻.\(^{17,19}\)

Zitnian and Sitaj in 1976 reported calcification of the cervical and lumbar discs in 33 cases with "articular chondrocalcinosis," and concluded that "the basis of the arthropathy and vertebropathy are incrustation of hyaline and fibrous cartilage of the joints and spine with CPPD." However, no calcification in the yellow ligament was included. Identification of CPPD crystals in the yellow ligament of the lumbar spine was reported by Bywaters, et al., in 1971.\(^{3}\) A case with identified CPPD crystals in the cervical ligamenta flava in the absence of arthropathy was reported by Kawano, et al., in 1980,\(^{13}\) followed in 1981 by a report by Nagashima, et al.,\(^{24}\) with computerized tomography (CT) findings of the disease.

The present report deals with three cases of myeloradiculopathy due to CPPD crystal deposits in the cervical ligamenta flava, with a comprehensive review including nine previously reported cases.\(^{1,4,11-14,25}\)

Case Reports

Case 1

This 74-year-old woman had had diabetes mellitus and had been taking insulin since 1977.* She was admitted to Saitama Medical School Hospital on November 11, 1980, with complaints of clumsiness of both hands, numbness in the distal parts of her legs and arms, and pain radiating from the shoulder to all fingers of both hands upon neck flexion. About 15 months before admission she first noticed numbness in the right

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* This case was first reported by Nagashima, et al.,\(^{24}\) in Japanese. This English translation is reproduced with permission.
FIG. 1. Case 1. Plain cervical spine film (left), sagittal laminogram (center), and myelogram (right) showing abnormal opacities in the posterior spinal canal at C4–5 and C5–6 (arrows). These are observed more clearly on the laminogram (center). Myodil myelogram (right) shows partial blocks corresponding to the levels of the radiopaque lesions (arrows). (Reproduced from Nagashima, et al., 24 with permission.)

FIG. 2. Case 1. Computerized tomography at the C-5 vertebral level showing two round high-density areas protruding from the lamina into the spinal canal (arrows). The right one is larger than the left. Density of these areas ranges from +212 to +153 EMI units (mean +182 EMI units). (Reproduced from Nagashima, et al., 24 with permission.)

index and middle fingers which gradually progressed to all fingers and palms bilaterally, then to plantar aspects of the feet over the next 9 months. Two months prior to admission she experienced difficulty in writing and sewing, followed by pain radiating into all fingers on flexing her neck. She had no history of spinal injury or joint pain. Family history was noncontributory.

Examination. She was 140 cm in height and 39 kg in weight. General physical examination showed no abnormalities. Blood pressure was 150/80 mm Hg, and pulse rate 72/min. Neurologically there was marked weakness of the intrinsic hand musculature, with atrophy of thenar, hypothenar, and interosseal muscles. Deep tendon reflexes were exaggerated in all four extremities except for the biceps reflexes, which were more hypoactive on the right side. Moderate hypesthesia was noticed in the area between the C-6 and C-8 dermatomes. Below T-10 she had hypalgesia and cold dysesthesia. Vibration sense was markedly impaired below L-1. Gait was spastic. Flexion of the neck with the shoulder pulled backward elicited severe pain in the neck and shoulder radiating down into all fingers of both hands. There was no sphincter disturbance.

Complete blood count on admission was within nor-
Calcified deposits in ligamenta flava

Fig. 3. Surgical specimen from Case 1 viewed from inside (left), and soft-tissue x-ray film of the specimen (right). Five hemispherical nodules are noted in the ligamenta flava between the laminae of C4-5, C5-6, and the right side of C6-7 (arrows). The soft-tissue x-ray film clearly demonstrates radiopaque lesions at the corresponding levels. The right-sided C5-6 lesion is larger than the left which confirms the computerized tomography findings (Fig. 2). The CT density of the areas ranged from +212 to +153 EMI units (mean +182 EMI units). The right high-density lesion was larger than the left. X-ray films of the remainder of the skeleton revealed no abnormality.

Operation. In order to perform studies of the lesions, including detailed anatomical relationship with the surroundings, en bloc removal of the affected ligamentum flavum with the laminae above and below was planned. On November 26, 1980, bilateral facetectomy was first made at C4-5, C5-6, and a C-7 laminectomy was performed. Longitudinal gutters were made on both sides of the C-4, C-5, and C-6 laminae by air drill and Kerrison punch. The cortical bone was sclerotic, and the cancellous bone was more rarefied than usual. The yellow ligament was cut between C-3 and C-4. The block from C-4 to C-6 elevated spontaneously and was reflected laterally. Any slight adhesions were cut, and en bloc removal was done. The dural sac then showed marked dorsal migration and pulsation.

Postoperative Course. The patient’s postoperative course was uneventful except for a raised blood sugar content and mild root irritation. By the next morning, clumsiness of both hands had almost resolved. She had 221 mg/dl of blood sugar, which was controlled by insulin. On the third postoperative day, upon changing posture, symptoms of root irritation suddenly developed. Re-exploration under local anesthesia revealed tethered roots due to marked dorsal migration of the dural tube. Enlargement of the facetectomy with removal of extra bone at the axilla and shoulder of the roots was followed by immediate disappearance of the root pain. The cold dysesthesia, hypalgesia, and pallohypesthesia recovered to normal, and 80% of the numbness of the arm and leg had cleared at the time of discharge on December 27, 1980. A follow-up period of 2 years and 2 months revealed complete recovery of neurological symptoms; the patient had skilled finger movements when sewing or writing. Biochemical study still showed slightly increased parathyroid hormone and alkaline phosphatase in the blood with a normal level of Ca and inorganic P.

Pathological Examination. The specimen (Fig. 3) consisted of the laminae of C4–6 and the ligamenta flava. There were five glistening yellow hemispherical nodules in the ligamenta flava between the laminae of C4-5, C5-6, and the right side of C6-7 (arrows). The soft-tissue x-ray film clearly demonstrates radiopaque lesions at the corresponding levels. The right-sided C5-6 lesion is larger than the left which confirms the computerized tomography findings (Fig. 2). The CT density of the areas ranged from +212 to +153 EMI units (mean +182 EMI units). The right high-density lesion was larger than the left. X-ray films of the remainder of the skeleton revealed no abnormality.

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FIG. 4. Case 1. Photomicrographs showing the ligamentum flavum, the lamina above (L-A), and the lamina below (L-B) the lesion. A: An accumulation of fine granular amorphous substance with widely dispersed elastic fibers (E1) lies adjacent to the lamina above (L-A) the lesion. Van Gieson, × 18. B: Coarse granular deposits (arrowheads) are seen in the elastic fiber (E1) adjacent to lamina below (L-B) the lesion. Note that the fibers are not dispersed in this section. Van Gieson, × 18. C and D are enlargements of areas in A. Van Gieson, × 36. C: Mature (arrowheads) and immature or "earlier" (arrows) lesions are seen pushing aside the fibers, suggesting "expansive growth." D: Numerous chondrocytes (arrows) are noted around the lesion. E and F: Dark-stained finely granulated, amorphous substance and coarse granules. In F (enlarged from E) can be seen hemispherical nodules of variable size in a layer of coarse granules. An egg-shaped, partially ossified chondrocyte is shown in inset. Von Kossa hematoxylin, × 36 (E), × 180 (F), and × 360 (inset). (Reproduced from Nagashima, et al., with permission.)
Calcified deposits in ligamenta flava

FIG. 5. Case 1. Scanning electron micrograph showing the morphology of the crystals. The rod- or pillar-shaped crystals are 0.3 to 9 \( \mu m \) in length and 0.1 to 3 \( \mu m \) in width. The fragmented elastica (EL) is also seen. \( \times 2600 \). (Reproduced from Nagashima, et al., \textit{24} with permission.)

nodules located on either side of the midline in the ligamentum flavum. Their consistency was elastic and firm. Of the five, two were at C4-5, almost symmetrical, measuring 8 \( \times \) 8 \( \times \) 3 mm; two at C5-6, the right nodule being the larger at 10 \( \times \) 10 \( \times \) 4 mm, and the left 10 \( \times \) 8 \( \times \) 4 mm; and one at C6-7 on the right, which was the smallest nodule at 4 \( \times \) 4 \( \times \) 2 mm. Soft-tissue x-ray films clearly showed: 1) radiopaque lesions corresponding to the nodules; 2) the right nodules larger than the left; and 3) the nodules lying caudal to the lamina cephalad and the deposition of the radiopaque substance lying along the longitudinal fibers of the ligamentum flavum approaching the lamina caudad. The superior margins of the nodules were better outlined than the inferior margin, where numerous small deposits were still visualized. The findings strongly suggested that the deposition had arisen at the area adjacent to the lamina above and may have grown downward. On the cut surface the nodules were composed of fine yellowish-white granules accumulated within the yellow ligament. They were fragile, chalk-like, and softer than bone.

An overall histological view of the lesion including the laminae above and below the lesion is shown in Fig. 4A to D. The lesions lay within the parallel arrays of elastic fibers, some of which were disrupted. The lesions' abnormal deposits were pushing aside the elastic fibers, suggesting that the deposits were enlarged by "expansive growth." The deposits contained two types of materials, both positive for calcium on von Kossa staining (Fig. 4E and F). One type contained many fragments of coarse angulated material, and the other finely granulated or amorphous material. The finer material tended to be deposited in the periphery of the lesion where elastic fibers still remained dispersed and chondrocytes were seen scattered on the interfiber matrix (Fig. 4C and D). The coarser material tended to be accumulated in the central area of the lesions where no elastic fibers remained and where egg-shaped and partially ossified chondrocytes were seen (Fig. 4F). However, there were no ossified areas or completely ossified cells such as are usually observed where this type of chondrocytic metaplasia is taking place, and no inflammatory reaction was noted. In areas adjacent to the lamina above the lesion, there were dispersed elastic fibers, widened interfiber matrix, and chondrocytes suggesting "precursor ground" for future deposits. In areas adjacent to the lamina below the lesion, however, neither dispersed fibers nor widened interstitium were observed. This finding strongly suggested that the lesion had enlarged from above downward as noted on the soft-tissue x-ray film of the specimen (Fig. 3 right).

With a polarized light microscope, the finely granulated substance was revealed to be positively birefractive crystals with a length of 0.3 to 9 \( \mu m \), and a width of 0.1 to 3 \( \mu m \). Fragmented elastica are also seen (Fig. 5). The identification of crystals was performed both by energy-dispersive x-ray microanalysis in a scanning electron microscope \textit{26} and by selected-area electron diffraction using a transmission electron microscope. The x-ray spectrum of elements contained in the crystals was almost identical with that of calcium pyrophosphate (Ca\(_2\)P\(_2\)O\(_7\) \textit{right}) by energy-dispersive x-ray microanalysis. The crystals in the tissue contain calcium and phosphorous, and the x-ray intensity ratio of calcium and phosphorous of the crystals are almost identical to that of Ca\(_2\)P\(_2\)O\(_7\). (Reproduced from Nagashima, et al., \textit{24} with permission.)

FIG. 6. X-ray spectra of the crystals in the tissue (left) and of pyrophosphate (Ca\(_2\)P\(_2\)O\(_7\)) (right) by energy-dispersive x-ray microanalysis. The crystals in the tissue contain calcium and phosphorous, and the x-ray intensity ratio of calcium and phosphorous of the crystals are almost identical to that of Ca\(_2\)P\(_2\)O\(_7\)). (Reproduced from Nagashima, et al., \textit{24} with permission.)
Fig. 7. Debye-Scherrer rings composed from the electron diffraction patterns of crystals by selected-area electron diffraction. Heavy dots are main diffraction spots obtained commonly from all crystals. The diffraction pattern of crystals coincided nearly to that of CPPD in ASTM Card 22-534. $L = \text{diameter of Debye-Scherrer ring}; dA^* = \text{calculated lattice distance calculated from } dA^* = (0.037 \times 59.67 \times 6)/Lx (A^*)$. Accelerating voltage: 100 kV; camera length: 59.67 $\times$ 3 cm.

Case 2

This 61-year-old man first noticed pain radiating from the neck to all four extremities when he hyperextended his neck 1 year before admission to the Iesasaki City Hospital. Eight months later he experienced occasional severe attacks of neck and shoulder pain on getting up from bed in the morning. Two months prior to admission he noticed cold dysesthesia, first in the distal part of the left leg, then in the right; this disorder gradually progressed to both entire legs and was associated with difficulty in walking, pain radiating from the neck to both arms on sneezing and coughing, and clumsiness of both fingers. There was no history of craniovertebral trauma or arthritis. Family history was noncontributory.

Examination. The patient was admitted on April 13, 1981, with restricted neck motion, particularly on extension, which produced severe pain radiating into all four limbs. Deep-tendon reflexes were exaggerated in all the limbs with bilateral Hoffmann, Trömmer, and Babinski signs. Gait was spastic. There was marked clumsiness of both hands without fasciculations or atrophy of the arms or intrinsic hand musculature. Slight hypesthesia to pain and temperature was noticed below T-4 and in both arms, more marked in the distal part of the limbs. Vibration sense was especially impaired below L-1 and there was marked cold dysesthesia in both legs and hands.

Complete blood count and urinalysis on admission were within normal limits. Blood chemistry showed Ca 4.8 mg/dl, inorganic P 3.6 mg/dl, Mg 1.6 mg/dl, Cu 137 $\mu$g/dl, uric acid 5.5 mg/dl, and Fe 107 $\mu$g/dl. All of these findings were within normal range for our laboratory. C-reactive protein, rheumatoid factor, and Wassermann reaction tests were negative. Glucose tolerance test revealed that the patient was not diabetic. The level of parathyroid hormone in the blood was normal at 0.2 ng/ml. Test for HLA B27 was reported as negative. Analysis of CSF obtained by lumbar puncture showed an opening pressure of 130 mm H$_2$O with 2 cells/cu mm, a protein content of 150 mg/dl, and a glucose level of 58 mg/dl. Queckenstedt's test elicited slow elevation of pressure.

X-ray examination of the cervical spine showed spondylotic disc narrowing and spurs at C5-6, elliptical radiopaque nodules of 4 $\times$ 10 mm at C3-4, and larger nodules of 6 $\times$ 11 mm at C4-5 (Fig. 8A–C). The nodules at C3-4 were shown to be situated almost symmetrically, while at C4-5 the right nodule was larger and more dense than the left (Fig. 8D). Complete bone survey and spinal angiography revealed no abnormalities. Myelograms showed extradural compression corresponding to the spondylotic spur and to the nodules.

Operation. On April 28, laminectomy was performed from C-3 to C-5. Calcified nodules, as shown on x-ray films, were found in the ligamenta flava of C3-4 and C4-5; the right C4-5 nodule was the largest. They were fairly well demarcated from the normal ligament and were composed of fine whitish granules of the consistency of pumice. There was no adhesion to the dura.

Postoperative Course. The patient showed marked improvement of neurological signs and symptoms and was discharged on June 14, 1981. At follow-up examination 22 months after surgery, the patient is completely free from his preoperative symptoms. Histological studies and identification of crystals were very similar to those in Case 1. The crystals were identified as CPPD.

Case 3

This 65-year-old woman, who was a known diabetic with numerous complications, was referred from the Department of Neurology, Saitama Medical School Hospital. She had a 12-year history of diabetes mellitus, a 10-year history of chronic hepatitis, hypertension and intermittent urinary tract infections, vaginal and cutaneous candidiasis, bronchopneumonia, auditory loss, and mild incomplete polyneuritis affecting mainly the lower limbs. About 5 months prior to admission, the leg pain worsened and the patient developed paraplegia, monoplegia of the right arm, and difficulty in micturition. She had no history of spinal injury. Family history was noncontributory.

Examination. On admission on July 10, 1982, the patient had severe spastic tetraparesis, loss of all sensory modalities below C-5, diabetic neuropathy of both legs, a decubitus ulcer, and diabetic retinopathy. Cystometric examination revealed a flaccid neurogenic bladder. There was cardiomegaly with moist rales on both lung fields, which resolved later with systemic antibiotic administration. Hepatosplenomegaly, ascites, and cutaneous venous collaterals were not detectable.
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FIG. 8. Case 2. Plain cervical spine film (A), sagittal laminogram taken at the midline (B), sagittal laminogram taken 3 mm to the right of the midline (C), and coronal laminogram (D). Elliptical radiopaque shadows at the level of C3-4 (4 x 10 mm) and C4-5 (6 x 11 mm) (arrows) in the plain film (A) are observed more clearly in the laminograms (B and C). The oval lesions at C3-4 (upper arrow, D) are located symmetrically, while at C4-5 (lower arrows, D), the right-sided lesion is larger and denser, with asymmetry of the lesions. Therefore, the right-sided laminogram (C) clearly shows the lesion at C4-5.

Complete blood count and urinalysis on admission were within normal limits, except for normochromic anemia and evidence of urinary tract infection with positive findings of Candida albicans and glycosuria. Severe hyperglycemic reaction was noted after a 50-gm glucose tolerance test, with 320 mg/dl before insulin therapy, and again after insulin therapy, with 590 mg/dl at 1 hour, 624 mg/dl at 1½ hours, 616 mg/dl at 2 hours, and 516 mg/dl at 3 hours. This condition was well controlled in the Neurology Department. Blood levels of Ca, inorganic P, uric acid, creatinine, total cholesterol, total protein, gamma glutamic pyruvic transaminase (GPT), and cholinesterase were all within normal range. Blood levels of glutamic oxalo-acetic transaminase were increased to 141 IU (normal less than 40 IU), GPT to 157 IU (normal less than 35 IU), alkaline phosphatase to 95 mU/ml (normal 30 to 85 mU/ml), and urea nitrogen to 26 mg/dl (normal 7 to 20 mg/dl). Serum hepatitis Bs antigen and antibody were negative. These data indicated non A and non B chronic hepatitis. Analysis of CSF obtained by lumbar puncture showed 3 cells/cu mm, a total protein content of 80 mg/dl, a sugar level of 88 mg/dl (simultaneously obtained blood sugar 144 mg/dl), and Cl 124 mEq/liter. Wassermann test of the CSF and serum was negative.

X-ray films showed a developmental narrow canal, with an anteroposterior diameter of 16 mm at C-1, 14 mm at C-2, and 11 mm at C-3, C-4, and C-5. There was spondylotic osteoarthrosis of the C3-4 apophyseal joints with facet hypertrophy (Fig. 9A). Laminograms revealed a segmental type of ossification of the posterior longitudinal ligament (OPLL) behind the C-5 body, extending up along the protruded C4-5 disc (Fig. 9B), and a round dense shadow suggesting a calcified nodule between C3-4, close to the C-3 lamina (Fig. 9C). Metrizamide myelography showed a filling defect at C3-4 due both to the calcified nodule (dorsal defect) and to the hypertrophied facets (ventral defect) (Fig. 9D). X-ray films of the thoracic and lumbar spine showed ossification of the anterior longitudinal ligament of the thoracic and lumbar spine, which is frequently observed in patients with OPLL. The patient was placed immediately in skeletal traction with Crutchfield tongs for about 1½ months, and responded with slight increase of muscle strength in both legs with aggravation of pain in the right shoulder and arm corresponding to the dermatomes of C-4, C-5, and C-6. Operation was de-
layed until her multiple other symptoms were under control.

Operation. Because of radicular pain at C-4, C-5, and C-6, transverse myelopathy, and a probable calcified nodule within the C3-4 ligamenta flava, a facetectomy overlying the roots of C3-629 and en bloc removal of the C2–T1 laminae and yellow ligament (including the calcified lesions) were carried out on August 23, 1982. The C3–4 facetectomy revealed that the dura lay exceptionally deep over the C-4 roots due to facet hypertrophy. Following en bloc removal, fine fibrous strands lay between the inner surface of the yellow ligament and the dura, and good pulsatile motion with marked dorsal migration of the entire dural tube ensued. There was loss of 500 ml of blood, which was replaced by transfusion. Frequent aspiration of exudate in the airway was necessary, but the PaO$_2$ and PaCO$_2$ remained within normal limits. Occasional arrhythmia was recorded on the electrocardiogram, without any hypotensive episode.

Postoperative Course. By the next morning, pain in the right arm and shoulder had disappeared, and the level of analgesia began to fall from C-5 to T-4 and T-6 on the right and left, respectively. Blood sugar rose to 300 mg/dl with intense glycosuria the next day, which was controlled by administration of regular insulin. Mucous secretion from the respiratory tree was so abundant that tracheostomy was required. Chest x-ray disclosed massive atelectasis of the lower lobe of the right lung on the 4th postoperative day, followed by solidification of the entire right lung. This extensive pneumonia was not controllable by heavy doses of antibiotics, cardiotherapy, postural drainage, diuretics, or oxygen therapy. The patient suffered cardiac failure, hypoxic brain damage with coma, and died on the 33rd postoperative day. No autopsy was obtainable.

Pathological Examination. The specimen (Fig. 10 left) consisted of the C3–4 laminae with the underlying ligamentum flavum showing two almost symmetrical, hemispherical, glistening yellow protrusions with diameters of about 5 mm. Their appearance was similar to that seen in Fig. 3 left. X-ray films of the en bloc specimen showed two radiopaque lesions corresponding to the nodules under the C-3 lamina. The radiopaque materials were arranged along the longitudinal fibers of the ligament running down to the C-4 lamina (as was
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Fig. 10. Surgical specimen viewed from inside (A) including the laminae of C-3 and C-4 (3 and 4 in A) and ligamenta flava above the C-3, between the C3-4, and below the C-4 laminae. Two hemispherical nodules were seen in the yellow ligament at C3-4. White vertical lines indicate cut planes from midline (dotted line in A) to the left, making six slices, which were numbered from 1 to 6 in A and B. B: Macroscopic (upper) and soft-tissue x-ray (lower) views of the slices. “Inside” indicates the surface facing the inside of the spinal canal. In Slices 2 and 3, well circumscribed white nodules (black arrows) and corresponding radiopaque round shadows are visualized. The radiopaque shadows are most prominent in the paramedian Slices 2 and 3. An additional small calcified nodule is seen in the yellow ligament below the C-4 lamina in Slice 3. Note the similarity of the soft-tissue x-ray appearance of the nodule in the slices with the preoperative laminograms in Fig. 9C.

Discussion

In all three cases, oval or triangular lesions were noted in the posterior aspect of the cervical canal on the lateral plain x-ray films. This was seen most clearly in the laminograms, both sagittal (Cases 1 and 3) and coronal (Case 2). The lesions were situated in close proximity to the lamina above. They occurred independently or in association with cervical spondylosis (Cases 2 and 3) or with OPLL (Case 3), with or without a developmental narrow canal. Awareness of the lesions may be important in treating cervical spondylosis, especially by anterior decompression and disectomy alone.

Review of the nine other reported cases (Table 1) revealed oval or elliptical areas of radiodensity from C2–3 down to C6–7, most frequently at C5–6 (Table 2). These lesions were also found independently or in association with cervical spondylosis or OPLL. Why did our Case 1 show a triangular radiodensity formation? Typical appearance of CPPD deposits in the hyalin or fibrocartilage on the knee is demonstrated as heavy linear or punctate areas of radiodensity. In our surgical specimen, x-ray examination showed central and peripheral linear densities, suggesting that the deposits occurred along the
## TABLE 1
Summary of reported cases of myeloradiculopathy with calcified cervical ligamenta flava*

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Age (yrs), Sex</th>
<th>Radiographic Level of Lesion</th>
<th>Associated Spine &amp; Joint Disease</th>
<th>Endocrine Metabolic Disorder</th>
<th>Crystal Type</th>
<th>Signs &amp; Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ellman, et al., 1978</td>
<td>70, M</td>
<td>not mentioned</td>
<td>severe CPPD deposit in knee joint</td>
<td>elevated serum Ca, normal parahormone</td>
<td>CPPD</td>
<td>arm weakness</td>
</tr>
<tr>
<td>Kamakura, et al., 1979†</td>
<td>70, F</td>
<td>C5–6, C6–7 oval dns</td>
<td>knee arthropathy</td>
<td>pseudogout, linear dns in knee menisci</td>
<td>not identified</td>
<td>pain radiating to ulnar side of hands on neck extension, restricted neck motion, spastic gait, marked impaired vibration sense</td>
</tr>
<tr>
<td>Jyotoku &amp; Harada, 1980</td>
<td>61, F</td>
<td>C4–5, C5–6, C6–7 oval dns</td>
<td>minimal cervical spondylisis</td>
<td>none</td>
<td>Ca₃(PO₄)₂(OH)</td>
<td>numbness in ulnar side of arms, restricted neck motion, atrophy of lumbrical &amp; interosseus muscles, hyporeflexia of biceps &amp; triceps, hyperreflexia of knee jerks</td>
</tr>
<tr>
<td>Kawano, et al., 1980</td>
<td>63, F</td>
<td>C3–4, C4–5, C6–7 oval dns</td>
<td>minimal cervical spondylisis</td>
<td>none</td>
<td>CPPD</td>
<td>clumsiness of hands, spastic gait, moderately impaired vibration sense</td>
</tr>
<tr>
<td>Kida &amp; Tatabata, 1981</td>
<td>76, F</td>
<td>C2–3, C3–4, C5–6 oval dns</td>
<td>none</td>
<td>none</td>
<td>not identified</td>
<td>sudden pain radiating to all limbs, tetraplegia, gradual recovery for 2 mos; numbness in legs, clumsiness of hand, atrophy of intrinsic hand muscles, spastic tetraparesis, loss of vibration sense &amp; topognosis, hypotonia below T-10</td>
</tr>
<tr>
<td>Fujiwara, et al., 1982</td>
<td>72, M</td>
<td>C4–5, C5–6, C7: 2 round hd areas</td>
<td>OPLL, C3–6</td>
<td>not mentioned</td>
<td>a kind of calcium phosphate, not CPPD</td>
<td>weakness of rt leg, clumsiness of rt fingers, spastic tetraplegia, loss of all sensory modalities below C-4, dysuria</td>
</tr>
<tr>
<td>Akino, et al., 1983</td>
<td>64, F</td>
<td>C6–7, CT: 2 round hd areas</td>
<td>none</td>
<td>none</td>
<td>not identified</td>
<td>tender restriction of neck movement, hypalgia in distal four extremities</td>
</tr>
<tr>
<td>Nakajima, et al., 1983</td>
<td>60, F</td>
<td>C3–4, C4–5, C5–6, C6–7 cervical spondylisis</td>
<td>none</td>
<td>not identified</td>
<td></td>
<td></td>
</tr>
<tr>
<td>66, F</td>
<td>C5–6, C6–7 anterior spur at C4–5</td>
<td>none</td>
<td></td>
<td></td>
<td>Ca₃(PO₄)₂(OH)</td>
<td>It spastic hemiparesis due to previous cerebrovascular disease, clumsiness of rt hand</td>
</tr>
<tr>
<td>Nagashima, et al., 1984</td>
<td>74, F (Case 1)‡</td>
<td>C4–5, C5–6, triangular CT appearance with 2 round hd areas</td>
<td>none</td>
<td>mild DM, increased parathormone &amp; alkaline phosphatase</td>
<td>CPPD</td>
<td>clumsiness of hands, pain radiating to all fingers on neck flexion, spastic tetraparesis, marked impaired vibration sense</td>
</tr>
<tr>
<td>61, M (Case 2)</td>
<td>C3–4, C4–5, oval dns</td>
<td>moderate cervical spondylisis</td>
<td>none</td>
<td></td>
<td>CPPD</td>
<td>clumsiness in both hands, pain radiating into four limbs on hyperextending neck, marked impaired vibration sense below T-4, spastic gait</td>
</tr>
<tr>
<td>65, F (Case 3)</td>
<td>C3–4, oval dns</td>
<td>OPLL in C-5, moderate cervical spondylisis</td>
<td>none</td>
<td>moderate DM, chronic hepatitis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Abbreviations: dns = densities; DM = diabetes mellitus; OPLL = ossification of posterior longitudinal ligament; hd = high density; CPPD = calcium pyrophosphate dihydrate; CT = computerized tomography.
† In Case 2 of Kamakura, et al., the surgical specimen revealed ossification of the ligamenta flava with bone marrow formation, so that patient was not included.
‡ Case 1 was abstracted and included in English translation from Nagashima, et al., with permission.
Calcified deposits in ligamenta flava

TABLE 2

Levels of affected ligamenta flava in 12 cases of myeloradiculopathy*

<table>
<thead>
<tr>
<th>Vertebral Level</th>
<th>No. of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>C2-3</td>
<td>1</td>
</tr>
<tr>
<td>C3-4</td>
<td>5</td>
</tr>
<tr>
<td>C4-5</td>
<td>6</td>
</tr>
<tr>
<td>C5-6</td>
<td>7</td>
</tr>
<tr>
<td>C6-7</td>
<td>6</td>
</tr>
</tbody>
</table>

* Nine patients had multiple levels affected.

longitudinal fibers (Fig. 3). A round dense area in the paramedian slices was seen as irregular linear spots in the peripheral sagittal slices (Fig. 10). This may indicate that there are transitional shapes between a “mature” round shape and “immature” linear shape. The larger the deposit, the more hemispherical and round it becomes.

The CT appearance noted by us in 198124 consists of almost symmetrical round areas of density in continuity with the internal surface of the lamina and with a lower attenuation value of the lesion than that of the adjacent intact laminae. Akino, et al.,1 and Fujiwara, et al.,7 showed similar CT pictures but with different attenuation values of the lesion. In our Case 1, the preoperative lesion density was +212 to +153 EMI units, with a mean of +182 EMI units (using an EMI scale of −500 for air density, 0 for water density, and +500 for bone density). In the surgical specimen from Case 3, the density was +201 EMI units in the lesion and +440 EMI units in the adjacent lamina (Fig. 10B). In the case of Fujiwara, et al.,7 the density was +800 to 1000 Hounsfield units in the lesion, and +900 to 1000 in the adjacent lamina. This discrepancy may be due to the presence of different calcium phosphates (not CPPD) in the lesions (Table 1). No attenuation value was mentioned in the case reported by Akino, et al.,1

Although the symptoms differ, depending upon the coexistence of other spine disorders, the initial symptoms of patients without other spine disorders1,4,11-14,24,25 include 1) clumsiness of the hands, and pain radiating into the arms or all four extremities upon neck extension and flexion; 2) restriction of neck movement; followed by 3) weakness of the arms and legs, atrophy of the intrinsic hand musculature, spastic tetraparesis, and hypesthesia with more marked impairment of the posterior column modalities. On flexion or extension of the neck, mechanical stress may be exerted upon the numerous filaments of the posterior roots and upon the cord, resulting in severe pain radiating not only into the arms, but also to the whole body, with consequent stiff neck. The Taylor mechanism11 may contribute to produce the syndrome.

The etiology and pathogenesis of CPPD deposition in the ligamenta flava has not been clarified. Histological findings of identified CPPD crystals deposited in the ligamenta flava were first reported in 1963, with the description of “crystal deposits being seen as large mulberry-like masses pushing aside the elastic fibers and as smaller (‘earlier’) accumulations appearing to develop in the unaltered tissue.3” This finding, observed in the lumbar area,3 coincides well with the present investigation, in that the crystal deposit did not occur on the elastic fiber but on the interstitium between the fibers (Fig. 4). In this location the deposit had enlarged, pushing aside the fibers and suggesting expansile growth, and smaller (“earlier”) deposits were also seen in the interfiber matrix (Fig. 4A, C, and D). Thus, the primary site of deposition is most likely in the interstitium.

Systemic and local factors in our three cases and in the nine previously reported cases are: 1) abnormal glucose metabolism (moderately severe and mild diabetes mellitus in two cases); 2) hyperparathyroidism (increased parathyroid hormone and alkaline phosphatase in our Case 1); 3) older female predominance (there were nine females and three males in the total series); 4) usual location at the C5-6 ligamentum flavum (Table 2), where the range of motion is greatest; and 5) fragmentation of elastic fibers and increase in the amount of collagenous tissue with advancing age.27 The systemic and local factors mentioned above may contribute to the “nucleation site of collagen nucleation theory”9 with altered interstitium, resulting in the crystal deposition. Among the crystals, it has been demonstrated that the hydroxyapatite often appears secondary to tissue damage, usually trauma, and continues to grow to form bone matrix, while the pyrophosphate, which exists in normal extracellular fluid, has a potent inhibitory effect on mineralization.5,6,9,30 In the present group of 12 cases with calcified cervical ligamenta flava (Table 1), two kinds of crystals (namely, CPPD4,11-24 and calcium hydroxide orthophosphate — Ca₃(PO₄)₂(OH) — were identified.11,25 It is likely that following the stage of initial cluster of calcium and phosphorous ions,9 various kinds of calcium phosphate crystals may be deposited depending upon the different nature of the interstitium; some CPPD, some calcium hydroxide orthophosphate, and some hydroxyapatite, with subsequent ossification of the yellow ligament.23

Acknowledgments

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