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A clinico-pathological study of cervical myelopathy in rheumatoid arthritis: post-mortem analysis of two cases

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Abstract Two patients who developed cervical myelopathy secondary to rheumatoid arthritis were analyzed post mortem. One patient had anterior atlanto-axial subluxation (AAS) combined with subaxial subluxation (SS), and the other had vertical subluxation (VS) combined with SS. In the patient with AAS, the posterior aspect of the spinal cord demonstrated severe constriction at the C2 segment, which arose from dynamic osseous compression by the C1 posterior arch. A histological cross-section of the spinal cord at the segment was characterized by distinct necrosis in the posterior white columns

and the gray matter. In the patient with VS, the upper cervical cord and medulla oblongata showed angulation over the invaginated odontoid process, whereas no significant pathological changes were observed. At the level of SS, the spinal cord was pinched and compressed between the upper corner of the vertebral body and the lower edge of the lamina. Histologically, demyelination and gliosis were observed in the posterior and lateral white columns.

Key words Rheumatoid arthritis · Cervical spine · Subluxation · Myelopathy · Necropsy

Introduction

The cervical spine is frequently involved in patients with rheumatoid arthritis. The three common patterns of instability seen in the rheumatoid cervical spine include anterior atlanto-axial subluxation (AAS), vertical subluxation of the atlas (VS), and subaxial subluxation (SS), or a combination of the above. Even in patients with severe instability, neurological manifestations are often absent or minimal. Therefore, relatively little information is available relating to pathological changes in the spinal cord with cervical myelopathy, mainly due to the rarity of this complication. There are, however, several reports of autopsies in patients with rheumatoid cervical spine [1, 2, 5, 15, 16].

In 1963, Martel and Abell [13] reported the cases of two autopsy patients who died suddenly from atlanto-axial dislocation, in which microscopic analysis of the spinal cord revealed congestion, recent hemorrhages, and

edema without significant inflammatory cell infiltration or demyelination. In 1967, Hopkins [9] reported four cases of tetraplegia as a result of SS. One of the four cases was analyzed post mortem. The autopsy report revealed narrowing of the spinal cord at the subluxated level due to compression by soft tissue, such as rheumatoid granulation tissue or an infolded ligamentum flavum. A histological examination of the spinal cord cross-section was not reported. Meijers and colleagues [14] in 1974 reported an autopsy case having VS with spastic paresis, and noted that the size of the spinal cord was markedly reduced at the level of the dens, which showed some bone proliferation and was surrounded by granulation tissue. They too did not mention histological changes in the compressed spinal cord. In 1977, Hughes [10] described the pathological findings in the spinal cord in two cases of SS at the C4/5 level with spastic paraparesis. Transverse slicing of the spinal cord showed a triangular cross-section at the C5 and C6 segments due to compression. Histological examination of the transverse sections revealed a large, irregu-

lar area of infarction involving the lateral white column and the anterior gray horn at the compressed segments. Upward Wallerian degeneration in the posterior columns and downward Wallerian degeneration in the lateral corticospinal tracts were also observed. In 1993, Henderson and colleagues [8] studied the histopathological changes in the brainstem and spinal cord in nine patients with myelopathy. They described that cranial nerve and brainstem pathology was rare in spite of the craniocervical compression, and that cord pathology occurred predominantly in the dorsal white matter, which was caused by subaxial degeneration.

In 1994, 11 patients with paralysis secondary to a rheumatoid cervical spine were analyzed post mortem by Delamarter and Bohlman [4]. Nine of the 11 cases revealed abnormal histology within the spinal cord, including necrosis, gliosis, and Wallerian degeneration. In the remaining two patients, the spinal cords were normal.

In the present study, two patients with long-standing rheumatoid arthritis involving the cervical spine, who had developed cervical myelopathy, were investigated post mortem. It is the purpose of this report not only to demonstrate the relation between the pre-mortem neurological symptoms and histological findings in the spinal cord, but to focus on the bony and soft tissue changes that cause compression of the spinal cord.

Materials and methods

Two autopsy cases of cervical myelopathy secondary to rheumatoid arthritis, for which roentgenographic and neurological records were available from the onset of myelopathy to death, were the subject of this study. Both patients had long histories of rheumatoid arthritis. One patient had suffered from AAS combined with

SS, and the other from VS combined with SS. Neurological classification according to the Ranawat system [17] revealed the former patient to be in class IIIB, and the latter in class II.

At the time of autopsy the entire cervical spine was excised including the cranio-cervical junction, and was suspended vertically in 10% formalin for 2–3 weeks, allowing the cervical spine to be fixed. After fixation, a sagittal section of the cervical column was made to observe the compression of the spinal cord caused by bony or soft tissue projections into the spinal canal. The spinal cord was then removed en bloc and divided into individual segments. Transverse sections of the spinal cord were stained by the Kluver-Barrera method, and surrounding tissues were stained by hematoxylin-eosin.

Results

Case 1

A 53-year-old woman who had suffered from rheumatoid arthritis since 1944 complained of pain in the occipito-cervical junction in 1968. Physical examination at that time revealed slight hypesthesia and hypalgesia on both upper limbs without apparent motor weakness or spasticity. Vibration sensation was severely impaired below the neck. A radiograph in neck flexion showed anterior AAS revealing 10 mm of the atlanto-dental distance. With extension of the cervical spine, complete reduction of the subluxation was noted. For treatment of this condition, posterior occipito-cervical fixation by wiring down to C4 was performed. Four months after the surgery, fusion between C1 and C2 consolidated, despite pseudoarthrosis at the other levels (Fig. 1A).

In May 1982, the same patient complained of numbness and weakness of the four extremities, which gradually progressed. Neurological findings were as follows:

Fig. 1 A, B Lateral radiograph of the cervical spine in case 1. **A** In 1968, posterior occipito-cervical fixation down to the level of C4 was performed for reducible atlanto-axial subluxation. Fusion between C1 and C2 consolidated despite pseudoarthrosis at the other levels. **B** In 1982, anteriorolisthesis of C2 on C3 resulted in severe quadriparesis. The involved facet joint of C2/3 was eroded

Fig.2 **A** Sagittal section of the cervical spine revealed complete disruption of the disc space and slippage between the C2 and C3 vertebrae. **B** Posterior aspect of the cord demonstrated severe constriction at the C2 segment ($\leftarrow a$) and mild indentation at the C3

lower segment ($\leftarrow b$). **C** Anterior aspect of the cord showed diffuse indentation and the empty anterior spinal vessels at the C4 segment ($\rightarrow$)

Fig.3 **A** Cross-section of the spinal cord at the C2 segment showed severe distortion on the right side. Distinct demyelination was noted in the right anterior and both posterior white columns. In addition, there was massive infarction on the right side of the anterior and posterior horns. **B** The spinal cord was markedly flattened at the C4 segment. Mild demyelination and gliosis were localized in the lateral and posterior white columns bilaterally

Fig.4 **A** The posterior-superior border of the C3 vertebral body protruded into the spinal canal ($\leftarrow$). Near the corner of the vertebral body, rheumatoid granulation tissue invaded the posterior longitudinal ligament and the vertebral body (H&E stain, $\times 20$). **B** Sagittal section of the anterior median atlanto-axial joint. The space between the anterior arch of the atlas (*) and the odontoid process (**) was filled with rheumatoid granulation tissue (H&E stain, $\times 20$)

severe hypalgesia on the four limbs and the trunk below the T10 level, exaggerated deep tendon reflexes of the four extremities, and the presence of pathological reflexes. Radiological study showed anteriorolisthesis of C2 on C3, and upward migration of the odontoid process (Fig. 1B). Treatment with halo vest apparatus failed to reduce these conditions, and progression of neurological symptoms resulted in severe quadriparesis and inability to ambulate (Ranawat class IIIB). The patient died of respiratory failure in September 1982.

Necropsy findings

A midsagittal section of the cervical spine showed complete disruption of the disc space and severe slippage between the C2 and C3 vertebrae. Osteosclerotic changes in both vertebrae were noted. The transverse ligament was absent. The spinal cord was pinched and compressed between the postero-inferior border of the C3 body and the lamina of C2. Space available for the cord at this level was only 6 mm. Neither infiltration nor thickening of the dura with granulation tissue were observed (Fig. 2A). The posterior aspect of the spinal cord demonstrated severe constriction at the C2 segment corresponding to the C1 posterior arch, and mild indentation at the lower C3 segment corresponding to the C2 lamina (Fig. 2B). The anterior aspect of the cord showed diffuse indentation caused by the upper and posterior border of the C3 body, and the empty anterior spinal vessels (Fig. 2C).

Microscopic findings

A histological section of the spinal cord at the C2 segment demonstrated severe distortion on the right side. Distinct demyelination and diffuse spongy degeneration were noted in the right anterior and in both posterior white columns, in contrast to much less demyelination in the lateral columns. There was massive infarction on the right side of the anterior and posterior horns, in which a remarkable neural tissue loss or chromatolysis of the persisting nerve cells was observed (Fig. 3A). The cord segment at C4 was markedly flattened, indicating 41% of the anteroposterior compression ratio [6]. Demyelination and gliosis were localized in the lateral and posterior white columns bilaterally, which were not very distinct despite the severe cord deformity (Fig. 3B). The spinal vessels were patent in all segments.

Figure 4A shows the posterior-superior border of the C3 body, which protruded into the spinal canal and corresponded to the compressed C4 segment. Near the corner of the vertebral body, rheumatoid granulation tissue with vascular proliferation and infiltration of chronic inflammatory cells, which had invaded into the posterior longitudinal ligament and the vertebral body, was evident. At

the anterior median atlanto-axial joint, the space between the anterior arch of the atlas and the odontoid process was filled with granulation tissue with infiltration of inflammatory cells. The posterior surface of the atlas was invaded by granulation tissue, and the bony plates were partially absorbed (Fig. 4B).

Case 2

A 50-year-old woman who had suffered from rheumatoid arthritis since 1955, complained of muscle weakness and numbness in all extremities in 1973. Physical examination revealed hyperreflexia and severely impaired tactile sensation in both the hands and below the level of T9. Vibration sensation was not completely absent (Ranawat Class II). Radiographic examination showed forward slippage of C3 on C4 and upward migration of the odontoid process. The minimum canal diameter was 9 mm at the C3/4 level. The distance between the tip of the dens and McGregor's baseline was 12 mm (Fig. 5). Subsequently, physical and radiographic findings did not deteriorate. In 1983 she died of heart failure resulting from mitral valve insufficiency.

Necropsy findings

A midsagittal section of the cervical spine revealed severe destruction of the intervertebral disc at the level of C3/4 and forward slippage of the C3 vertebral body. Ankylosis of the odontoid process, which protruded into the skull

Fig. 5 Lateral radiograph of the cervical spine in case 2. Note the forward slippage of C3 on C4 and upward migration of the odontoid process

Fig. 6 **A** Sagittal section of the cervical spine demonstrated severe destruction of the C3/4 disc space and protrusion of the odontoid process into the skull cavity. **B** Photograph of the base of the skull. Note severe basilar invagination of the odontoid process (←). **C** Posterior aspect of the spinal cord showed mild indentation at the C4 segment (←). **D** Anterior aspect of the cord revealed diffuse indentation and the empty anterior spinal vessels at the C4 segment (→)

cavity, with anterior margin of the foramen magnum was observed (Fig. 6A). A photograph of the base of the skull showed severe basilar invagination of the odontoid process, and the space available for the cord was 13 mm between the odontoid and the foramen magnum (Fig. 6B). The posterior aspect of the cord had a mild indentation at the C4 segment caused by the laminae of the C3 vertebra (Fig. 6C). Anteriorly the spinal cord was indented at the same segment, where the anterior spinal vessels were compressed and empty of blood (Fig. 6D).

Microscopic findings

The most damaged region was the C4 cord segment, where the spinal cord was markedly flattened anteroposteriorly, indicating 37% of the compression ratio. Severe necrosis extended throughout the entire gray matter on both sides, and cavity formation secondary to necrosis was noted. There was a trace of proliferation of glial cells in these necrotic areas. Massive demyelination and gliosis were present in the posterior and lateral white columns bilaterally. The anterior white column was spared on both sides. No obvious vascular abnormalities, such as occlusion or thick-walled vessels, were observed (Fig. 7A). Cephalad to the medulla oblongata, ascending Wallerian degenerations were traced in both posterior white columns

without any evidence of direct cord compression (Fig. 7B). At the C6 segment the shape of the cord was well preserved, and descending Wallerian degeneration was noted in the both pyramidal tracts, which could be detected down to the level of the C8 segment (Fig. 7C).

Figure 8 shows the sagittal section of the cranio-cervical junction. Bony fusion was observed between the odontoid process and anterior margin of the foramen magnum, which were surrounded by rheumatoid granulation tissue with proliferation of inflammatory cells.

Discussion

In patients with rheumatoid arthritis, cervical spinal cord compression may be caused by two different mechanisms. One is narrowing of the bony spinal canal caused by subluxation, and the other is intraspinal encroachment by soft tissue [11]. On lateral plain radiograms, cord compression by the former mechanism can be easily visualized, but the latter can not. At the atlanto-axial level, retrodental rheumatoid pannus can exert compression on the spinal cord. Grob and colleagues [7] reported that evidence of retrodental pannus was documented on MRI in 22 out of 76 patients who underwent C1-C2 posterior fusion. In both the cases presented here, retrodental pannus formation was insufficient to cause spinal cord compression, although the odontoid process was microscopically surrounded by rheumatoid granulation tissue. In both cases, stabilization of the upper cervical segment had been achieved as a result of atlanto-axial arthrodesis in the first patient and spontaneous bony ankylosis between the odontoid process and the occipital bone in the second patient. This fact suggests that intraspinal pannus may diminish and even disappear after immobilization of the

Fig.7 **A** Cross-section of the spinal cord at the C4 segment. Note flattening of the cord and destruction of the posterior and lateral white columns and the gray matter. **B** Cross-section of the medulla oblongata revealed ascending Wallerian degenerations in the both posterior white columns. **C** At the C6 segment, descending Wallerian degeneration was noted in both pyramidal tracts

Fig.8 Sagittal section of the cranio-cervical junction. Bony fusion was observed between the odontoid process (*) and the anterior margin of the foramen magnum (**), which were surrounded by rheumatoid granulation tissue (H&E stain, $\times 20$)

segments responsible for cervical motion. Grob and colleagues [7] analyzed the influence of atlanto-axial fusion on inflammatory retrodental pannus in 22 rheumatoid patients with pannus that had been verified on MRI. They stated that the retrodental pannus had significantly decreased or disappeared postoperatively in all patients.

At subaxial levels, not only rheumatoid pannus but also degenerated ligaments or a thickened dura can compress the spinal cord. Hopkins [9] suggested that one of the main causes of the cord damage was infiltration of granulation tissue into the dura, which subsequently became thickened and constricted. Kudo et al. [11] described five rheumatoid patients who developed cervical myelopathy at subaxial levels. At laminectomy, the cause of cord compression was found to be a band-like mass of soft tissue in the epidural space, which microscopically consisted of the ligamentum flavum invaded by a pannus of inflammatory granulation tissue. In the present cases the pathology differed. Bony displacement had narrowed the spinal canal sufficiently to compress the cord, and rheumatoid granulation tissue arising from the ligamentous attachment to the bone (enthesis) had invaded the posterior longitudinal ligament. If the invasion had spread to the intraspinal canal, the spinal cord could be compressed. Similar enthesopathy was frequently observed at the level of the intervertebral discs, where SS was not detected in pre-mortem radiographs.

Impairment of blood flow in the medullary vessels secondary to compression can potentially cause spinal cord damage. In our series, signs indicating vascular involvement, such as thick-walled vessels or occlusion, were not observed.

In the patient with AAS, the posterior aspect of the spinal cord demonstrated severe constriction at the C2 segment, which arose from dynamic osseous cord compression by the lamina of the atlas. A histological cross-section of the spinal cord at the segment was characterized by distinct necrosis in both posterior white columns and the right-side gray matter. Degeneration of the posterior columns corresponded with the impairment of vibration sensation. Delamarter and Bohlman [4] also revealed

that chronic mechanical compression due to AAS was associated with flattening of the cord and necrosis of both the gray matter and the posterior white columns.

Pathological findings at the SS level were similar in the two cases presented here. Both aspects of the spinal cord had a diffuse indentation caused by osseous impingement between the upper corner of the vertebral body and the lower edge of the lamina. Histologically, demyelination and gliosis were observed in the posterior and lateral white columns bilaterally. Henderson and colleagues [8] also revealed that the cord pathology was localized to the posterior white columns at the level of SS. Because the time from the onset of tetraplegia to death was short in the first patient, histological changes were not very distinct despite the observation that the spinal cord was severely flattened. In the second case, conversely, long-term disease duration resulted in severe degeneration of the spinal cord, despite only mild spastic paralysis. Furthermore, ascending and descending Wallerian demyelination was observed from the most damaged segment.

Demyelination in the posterior white column was common to the cross-sections of the spinal cord in both AAS and SS. Marks and Sharp [12] reviewed 31 patients with rheumatoid cervical myelopathy and noted that 20 out of the 31 had loss of vibration sensation. Meijers et al. [14] stressed a "marble sensation" with a disturbance of deep sensibility as one of the alarm signals indicating spinal cord damage. These findings imply involvement of the posterior white column. Deformed or inflamed peripheral joints often make it difficult to estimate motor weakness and to elicit reflexes. To detect subtle changes due to cervical cord lesions, particular attention must be paid to a disturbance of sensibility.

VS has the potential to result in neurological deficit and even sudden death from compression of the medulla oblongata [3]. In the present case, although the upper cervical cord and medulla oblongata demonstrated angulation over the invaginated odontoid process, the shape of the cord was well preserved and no significant pathological changes were observed except ascending Wallerian demyelination in the posterior white columns.

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