Case Report

Subacute human spinal cord contusion: few lymphocytes and many macrophages

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Study design: Clinicopathological correlation of three cases of subacute cervical spinal cord contusions.

Objective: To correlate the pathology of subacute cervical spinal cord injury (SCI) with imaging and clinical-functional studies, and to compare with findings from previous human SCI studies and animal models of SCI.

Setting: Department of Pathology, SUNY-Upstate Medical University, Syracuse, NY, USA.

Method: Post mortem pathology report.

Case report/Results: The clinical, radiological, and pathological findings of three cases of subacute spinal cord contusions are described in detail. The postinjury survival periods were 15, 20, and 60 days, respectively. Extensive microglia/macrophage infiltrations without significant lymphocytes are seen in all cases. Free radical injury as assessed by immunocytochemistry for 4-hydroxynonenal and nitrotyrosine showed a labeling pattern parallel to that of the macrophage distribution at 15 days, but no significant labeling in the injury sites at 20 and 60 days.

Conclusion: The present report, though limited in sample size, shows plenty of activated microglia/macrophages in human SCI up to 60 days postinjury. This observation not only confirms similar findings in previous studies, but also raises an intriguing question of potential interactions between these activated microglia/macrophages and the experimental therapy, proposed by some authors, of injecting exogenously activated macrophages to promote SCI repair. The small number of human SCI cases (in this as well as in most other single medical centers) available for detailed study illustrates the need for the establishment of a consortium of human SCI tissue banks.

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Introduction

The clinical, radiological, and pathological findings of three cases of subacute spinal cord contusions are described in detail. The postinjury survival periods were 15, 20, and 60 days, respectively. Similarities and differences to findings in animal models of spinal cord injury (SCI) are discussed, and the rationale for the establishment of a consortium of human SCI tissue banks to advance our understanding of human SCI is presented.

Case 1

The first patient was a 49-year-old white male with a history of smoking and alcohol abuse. He was driving

a tractor that was hit by a car, and he was thrown approximately 6 feet off the tractor with temporary loss of consciousness. Neurological examination showed that he was unable to move his lower extremities but had good strength in upper extremities. He had priapism and no rectal tone. Sensation was normal down to about the level of the nipple line. However, below the nipple line, he could feel only slight touch that was symmetric on both sides, a sensation of tingling. He was able to tell which toes was being touched but was unable to move. Initial computerized tomographic (CT) scan of his head, C-spine, T-spine, L-spine, abdomen and pelvis, were all reported to be negative. Repeat CT of the C-spine showed possible cord compression without evidence of fractures. Magnetic Resonance Imaging (MRI) showed a cord contusion at the C7–T1 vertebral level (Figure 1). He was put on methylprednisolone protocol and

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Figure 1 (a–d) T2 weighted MRI images show that there is increasing intensity in the cord at C7–T1 vertebral level associated with central area of slight signal loss (arrows in **a** and **b**, higher magnification in **c** and **d**, respectively). Overall, the size of the abnormal signal area is approximately 1.7 cm in superior–inferior dimension and 5 mm in the anterior–posterior dimension. These findings are consistent with cord contusion. A disruption of intraspinal ligament is also noted at this level

transferred to our hospital. His hospital course was complicated with aspiration pneumonia and he developed acute respiratory distress syndrome (ARDS) and renal failure. He became acutely bradycardic on the 12th hospital day and required cardiopulmonary resuscitation (CPR) twice during the next 2 days. The family decided to make the patient do not resuscitate (DNR), and he died 15 days after the accident.

Autopsy findings

Gross examination of the spinal cord after formalin fixation showed no obvious external hemorrhage or other lesions (Figure 2a–b). Palpation of the cord, however, revealed focal softening corresponding to the C7–T1 vertebral level. Serial transverse sectioning of the cord revealed focal petechiae and discolored cord parenchyma in the softened segments (Figure 2c–d). Microscopic examination of corresponding sections showed marked destruction of cord parenchyma with loss of neurons, axons and myelin in the softest portion of the contused cord (Figure 2e, middle two slices), and focal tissue destruction in the superior and inferior sections (Figure 2e). The superior–inferior extent of the most damaged cord parenchyma (Figure 2e, middle four sections, each cord slice is about 0.3 cm thick) is consistent with the most obvious signal abnormality in MRI imaging (Figure 1). Superior (Figure 2j) and inferior (Figure 2k) cord sections, about 5 cm away from the center of the contusion, appeared virtually normal, without obvious evidence of Wallerian degenerations.

The anterior portion of the cord appeared to suffer more damage than the posterior portion. This is consistent with contusion-compression due to temporary herniation of the intervertebral disc.

Immunocytochemistry performed on the section near the center of the lesion (marked with a star in Figure 2e) showed that virtually the entire cross section of the cord was filled with CD68-positive activated microglia/macrophages (Figure 2f). No appreciable lymphocytes are seen. Only a small number of viable astrocytes (positive for GFAP) were seen near the peripheral rim of the cord (Figure 2i). A weakly diffuse labeling pattern, matching that of CD68, was seen with antibodies to 4-hydroxynonenal (Figure 2g) and nitrotyrosine (Figure 2h) (markers of lipid peroxidation and protein nitration, respectively^{1,2}). Focal areas of white matter show demyelination as well as absence of immunocytochemical labeling by antibodies to CD68, 4-hydroxynonenal, nitrotyrosine and GFAP (Figure 2e–i).

Focal injury to the anterior column in a more superior section (boxed area in the top section in Figure 2d and e) with demyelination, axonal loss, and macrophage infiltration is shown at higher magnification in Figure 2l. Adjacent sections processed for immunocytochemistry shows that the lesion core is populated by many activated microglia/macrophages (positive for CD68) (Figure 2m) and negative for reactive astrocytes (positive for GFAP) (Figure 2n). Focal residual intact myelinated axons are found in the periphery of the contusion center, mainly in the subpial portions of the posterior column (Figure 2e, center section marked with a star, boxed area is shown at higher magnification in Figure 2o). The adjacent injured white matter is marked by massive microglia/macrophage infiltration (positive for CD68, boxed area in Figure 2f, shown at higher magnification in Figure 2p).

Case 2

The second patient was an 80-year-old woman who was involved in a car accident with temporary loss of consciousness. Her past medical history includes myocardial infarction, atrial fibrillation, and congestive heart failure. On admission, the patient was awake, alert, mildly confused and unsure of the date and location. She complained of pain all over but she could move all extremities without obvious deficits. Clinical and imaging studies revealed a left humeral neck fracture, right orbital fracture, right frontal subarachnoid hemorrhage, a C1 lateral mass fracture, and a C5–C7 subluxation with a nonhemorrhagic contusion involving C4–C6 cervical spinal cord (Figure 3). Her hospital course was complicated by an evolving active myocardial infarction and her condition continued to deteriorate. She died 20 days after the car accident.

Autopsy findings

Gross examination of the spinal cord revealed no obvious lesions externally or on transverse

Figure 2 (a–b) Posterior and anterior view of the spinal cord. Note the absence of grossly obvious lesion on the surface. Palpation of the formalin-fixed spinal cord, however, revealed focally soft region inferior to the cervical enlargement. Panels **a** and **b** are at the same magnification. (c–d) Serial sections of the spinal cord reveal focal petechiae within the soft cord parenchyma. Higher magnification of the cut surfaces is shown in **d**. (e) Corresponding paraffin sections of the spinal cord segments in **d** are shown in **e** stained with Solochrome cyanine (also known as Chromoxane cyanine R – CCR for myelin) and hematoxylin-eosin. Note the marked loss of myelin stain in the middle sections, and focal loss of myelin in the superior and inferior cord segments. (f–i) Results of immunocytochemistry study on the center segment (marked with a star in **e**) are shown in **f** (CD68), **g** (4-hydroxynonenal), **h** (nitrotyrosine), and **i** (GFAP), respectively. (j–k) Representative superior cervical segment is shown in **j**, and inferior thoracic segment is shown in **k**, each about 5 cm from the center of the contusion. Note the absence of any obvious pathology in these sections. (l–n) The anterior funiculus in a superior cord segment (boxed area in the top section in **e**) is shown at higher magnification in **l**, with focal demyelination, axonal loss, and macrophage infiltration. Adjacent sections stained for activated microglia/macrophages (positive for CD68) and reactive astrocytes (positive for GFAP) are shown in **m** and **n**, respectively. (o–p) Residual intact myelinated fibers in the posterior funiculus near the contusion center (boxed area in the center section in **e**, marked with a star) adjacent to injured white matter with massive macrophage infiltration (positive for CD68, boxed area in **f**) are shown at higher magnification in **o** and **p**, respectively. Panels **d**–**k** are at the same magnification. Panels **l**–**p** are at the same magnification

Figure 3 (a–d) Serial T2 weighted sagittal MRI images show that there is intervertebral disc bulging posteriorly at the C4–C5, C5–C6 and C6–C7 intervertebral disc space levels, most prominent at the C5–C6 and C6–C7 levels. Signal abnormality consistent with a nonhemorrhagic contusion is present in the spinal cord extending from the C4 vertebral body to the C6–C7 intervertebral disc space. Arrows in **b** correspond to axial image levels in **g**, **i**, **l**, respectively. (e–l) Serial T2 weighted axial images

sections. Microscopic examination of representative cervical cord sections, however, showed irregularly shaped patchy areas of subacute contusion involving mainly the posterior half of the cord (Figures 4 and 5). Immunocytochemistry shows an irregularly shaped ‘*lesion core*’ area involving both the white matter (posterior and lateral columns) and gray matter (posterior horns) that is marked by negative reaction for GFAP (Figure 4c) and positive reaction for CD68 (Figure 4d). This core is surrounded by a ‘*lesion surround*’ zone of strong GFAP immunoreactivity (Figure 5c–d). Increased IgG labeling (Figure 5e), indicative of breach of blood–spinal cord barrier, is present in the ‘core’ region matching the distribution of CD68 labeling pattern. A relatively weak diffuse labeling poorly distinguishable from background is seen with antibodies to nitrotyrosine or 4-hydroxynonenal. No significant lymphocytes are appreciated, with rare T-lymphocytes (immunoreactive for CD3) found within both the ‘*lesion core*’ and the ‘*lesion surround*’.

Case 3

The third patient was a 59-year-old man who had a fall. His past medical history was significant for epilepsy, atrial fibrillation, chronic obstructive pulmonary disease, and cerebrovascular accident that resulted in left side weakness. Although wheelchair-bound, he was able to move all four extremities before the fall. He fell forward out of his wheelchair and struck his head, and likely hyperextended his neck. On admission after the fall, the patient showed altered mental status and was unable to move his arms or legs voluntarily, and did not withdraw to pain. He did have 1/4 reflexes at his knees. He had no rectal tone and he was incontinent of bowel. He had low blood pressure and the systolic at times was in the upper 40s to the lower 50s. The overall clinical impression was consistent with central cord syndrome, and he was treated with steroids. Imaging studies indicated stenosis around C5 and C6 with cervical cord compression/contusion (Figure 6). His hospital course was complicated with pneumonia, renal failure, and

Figure 4 (a–b) H and E (a) and CCR (b) stained sections, respectively, show focal contusion in the posterior aspect of the cord. (c–d) Immunocytochemistry for GFAP (c) and CD68 (d), respectively, shows that the contusion core is negative for GFAP and positive for CD68

right cerebral infarction with subarachnoid hemorrhage. He died at 60 days after the cord injury.

Autopsy findings

Gross examination of the spinal cord revealed a focally hemorrhagic contusion on the posterior surface of the cervical cord. Microscopic examination of representative sections revealed Wallerian degeneration of the ascending tracts superior to the contusion and the descending tracts inferior to the contusion (as highlighted by a stain for myelin in Figure 7). Sections near the epicenter of the injury revealed subacute contusion with an irregularly shaped 'lesion core' extending in finger-like fashion superiorly and inferiorly into both white and gray matters (Figure 8). The 'lesion core', containing focal cystic spaces and marked by its negative reaction for GFAP (Figure 8b–c), is filled with numerous CD68-positive activated microglia/macrophages (Figure 8d). Many small CD68-positive cells are also seen in adjacent less injured neuropil, likely a

Figure 5 (a–e) Low magnification micrographs of H and E (a) and CCR (b) stained sections at a different level from that in Figure 4. Boxed area in (b) is shown at higher magnification in (c) revealing that the posterior horn and the lateral aspect of the posterior column are contused. Immunocytochemistry shows that the lesion core is negative for GFAP (d) but positive for IgG (e)

mixture of activated microglia and blood-derived macrophages. Again, no significant lymphocytes are seen, and no specific labeling is seen with antibodies to nitrotyrosine or 4-hydroxynonenal. Mild IgG labeling is seen in the 'lesion core'.

Discussion and summary of observations of these human SCI specimens

1. Typing and grading of SCI: one of the most cited recent studies of human SCI neuropathology has classified the SCI into four general groups based on the gross appearance and the extent of the injury: solid cord injury, contusion/cavity, laceration, and massive compression.³ Studies by other authors^{3–7} have largely affirmed these findings. The relationships between histopathological changes and the functional assessments, however, awaits further clarification, since any of these groups may be seen in patients who are classified clinically as either complete or incomplete SCI according to functional assessment of motor, and sensory deficits below the injured segments (eg, based on

Figure 6 (a–b) T2 weighted sagittal MRI images show severe spinal canal stenosis from the C3 to C6 vertebral body levels due to a combination of posterior vertebral body spurring and/or ligamentous calcification and facet hypertrophy. There is also a central and left paracentral disc protrusion at C3–C4 partially accompanied by osteophyte formation. There is neural foraminal narrowing at multiple levels. There is abnormal cord signal at the C4 vertebral body level (arrows in a–b) that may represent contusion or focal myelomalacia. Block arrow in a–b points to a relatively normal thoracic cord. (c–g) Serial T2 weighted axial (transverse) images. Images in c and f correspond to levels marked by arrows in a and b. (h) T2 weighted axial image at a more inferior cord level (block arrow in a and b) shows relatively normal signal

Figure 7 (a–c) Low power micrographs of sections stained with CCR (for myelin) show Wallerian degeneration of the ascending tracts in sections above the contusion (a), and of the descending tracts below the contusion (c). Sections near the epicenter (b) show focal cystic regions and a general pallor over the entire cross-section of the cord

American Spinal Injury Association (ASIA) Impairment Scale, also known as AIS scale).⁸

In the present report, the extent of the contusion correlated well with clinical presentation. Large contusion (eg, patient 1), that covers virtually the entire cross-section of the cord at the center the lesion, was associated with clinically ‘complete’ injury below the level of injury. On the other hand, grossly normal spinal cord but having histological evidence of patchy contusion injury was associated with clinically ‘incomplete’ injury (eg, patient 2). The SCI of patient 2 corresponds best to the ‘solid cord injury’ described by Bunge *et al.*³ Based on observations from previous studies as well as from the present cases, it is perhaps simpler to consider solid cord injury as a subtype of contusion, representing an acute/early phase of mild or moderate contusion. The massive compression can be considered as an acute or subacute severe contusion. Both solid cord injury and massive compression, if survived, could develop cysts (seen in many chronic SCI patients as well as in animal models) that can be considered as the late/chronic phase of contusion (eg, patient 3). Histopathology classification (diagnosis) of SCI thus would include only two major types: contusion and laceration, with additional descriptions in the diagnosis incorporating injury severity grading (eg, subtypes of contusion: solid cord, massive compression, cysts), location, and postinjury durations.

2. Pathology and imaging correlation: as illustrated in the present study as well as in many previous studies, MRI is one of the most effective means to evaluate SCI. Unfortunately, however, most SCI patients often do not

Figure 8 (a–d) Low power H and E (a) stained section near the contusion epicenter (same level as in Figure 7b) shows an irregularly shaped partially cystic area in the posterior aspect of the cord. A small cystic area is also seen on the left side of the micrograph. Boxed area in a is shown at higher magnification in b. Immunocytochemistry reveals that the contusion ‘lesion core’ is negative for GFAP (c) and positive for CD68 (d)

have follow-up MRI studies after the initial MRI on admission to the hospital. The MRI images in this report were all obtained just after admissions, and thus the extents of visible MRI abnormalities do not match completely to those observed pathologically in autopsy,

from 15 up to 60 days after injury. Periodic MRI study of SCI patients, in both subacute and chronic phases, using some of the newer MRI imaging methods (eg, functional MRI, spectroscopy, diffusion tensor imaging),^{9–12} would be very helpful to monitor the longitudinal progress and the visible extent of SCI on imaging for correlation with clinical findings. For example, it would be informative to learn how long it would take for a moderate or severe contusion to form cystic lesions. Moreover, direct correlation of more recent MRI images with autopsy histopathology would be very useful to correctly interpret abnormal findings in MRI.

3. White matter lesion: although clinically ‘complete’ SCI (patient 1) is associated with severe pathological changes involving a large cross-sectional area of the cord near the contusion center, superior and inferior cord segments only a short distance from the contusion center do not show obvious pathology at 15–20 days postinjury (patients 1 and 2). On the other hand, obvious Wallerian degeneration of long tracts is seen at 60 days postinjury (patient 3, Figure 7). This is consistent with previous reports that Wallerian degeneration in human SCI is a prolonged process that may last up to several months.^{13–15} Focal regions of white matter near the center of the contusion appear to be not only demyelinated but also show an absence of CD68, GFAP, 4-hydroxynonenal or nitrotyrosine labeling in the lateral and anterior columns (Figure 2e–i). These regions may correspond to demyelinated but viable axons as reported in previous SCI studies^{16,17} and could be potential therapeutic targets.^{18,19}

4. Free radical injury: although the free-radical injury, as labeled by immunoreactivity for nitrotyrosine and 4-hydroxynonenal, appeared to match the distribution of activated microglia/macrophages in the contused spinal cord of patient #1 with postinjury-duration of 15 days, similar immunoreactions in patients #2 and #3, with postinjury-durations of 20 and 60 days, respectively, showed no significant labeling. The reason could be due to either method error (eg, poor fixation, poor antibody reaction, or both), or due to true gradual disappearance of these antigens following injury. This observation may be compared with that in a rat model of experimental contusion of the brain² in which the immunoreactivity for these markers peaked within 48 h but became less intense by 96 h after injury. Our limited sampling, however, illustrate the need for more human SCI samples that must be examined in order to clarify the relationship between postinjury-durations with the severity and extent of free-radical injury. This temporal relationship likely will critically influence the therapeutic window designed to limit injury due to free radicals.

5. Lymphocytes and macrophages: as seen in the present report, irregularly shaped but well delineated ‘lesion cores’, marked by areas free of GFAP immunoreactivity and filled with numerous CD68-positive microglia/macrophages, extend superiorly and inferiorly from the contusion center of the clinically complete SCI at 15 days (patient 1) as well as in partial contusions of

both 20 and 60 days post injury (patients 2 and 3). This observation highlights the fact that there are very few lymphocytes but plenty microglia/macrophages at the injury sites in subacute human SCI. This observation is consistent with previous report in human SCI.²⁰ Recent studies have shown that injection of blood-derived macrophages activated exogenously may be beneficial in rodent models of SCI.^{21–24} However, much remains to be learned about the mechanisms involved in this apparent beneficial effect. Although this experimental therapy of injecting blood-derived macrophages for human SCI is now currently undergoing Phase II clinical trial,²⁵ reproducible results using this protocol in larger animal models of SCI, including primates, are disturbingly lacking. Moreover, no information is available regarding the possible interactions between the exogenously activated macrophages and the macrophage/microglia intrinsically activated by SCI. There is no doubt that caution must be exercised in the planning, initiation and conduct of human clinical trials in SCI.²⁶

6. Need for human SCI tissue banks: while much exciting discoveries based on animal models of SCI have been reported recently, verification and validation of similar findings in human SCI have been relatively lacking, probably because of a lack of human SCI specimens for research. There is currently no public funded tissue bank devoted to the collection of human SCI specimens in the USA. Owing to variation of injury types, severities, locations, and postinjury durations, the sample size of comparable SCI specimens from any single medical center (or tissue bank) likely will be small. However, if SCI tissue banks could be established in multiple regions such that a national or international consortium may be formed to pool the valuable resource of human SCI tissue, the sample size will increase rapidly for collaborative research studies.

Although logistical difficulties (eg, obtaining consents for tissue donation, medical-legal issues involved in SCI, and harvesting specimens for both pathology and biochemical studies) likely have been responsible for a lack of SCI tissue bank, these are not insurmountable problems. Good lessons may be learned from organ transplants donation network that has successfully harvested critically needed organs and tissues for thousands of patients. Similar strategies may be employed to establish the SCI tissue bank consortium that would be a major step toward achieving our ultimate goals of better understanding of the mechanisms of injury and repair in human SCI, and thereby enable formulation of better therapies, including both neuroprotective therapies for acute/subacute SCI, as well as restorative-rehabilitative therapies for chronic SCI patients.

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