Pathology of radiation myelopathy

R. J. BURNS, A. N. JONES, AND J. S. ROBERTSON

From the Royal Adelaide Hospital and the Department of Pathology,
University of Adelaide, Adelaide, South Australia

SUMMARY After noting the rarity of papers describing the pathology of delayed radiation necrosis of the spinal cord, the clinical and pathological findings from four cases are presented. The main pathological features are asymmetric demyelination of the lateral columns and to a lesser degree the posterior and anterior columns of white matter, with coagulative necrosis at the level of irradiation which affected the grey matter to a lesser degree. There is ascending and descending secondary tract degeneration, and poor glial response in the lesions themselves. Vascular changes, mainly hyaline thickening of arteriolar walls, are present, but not in degree sufficient to explain the primary lesion. The discussion of the pathogenesis of the myelopathy weighs the merits of a primary vascular lesion against those of a primary effect of the radiation on neural tissue. The latter is favoured.

The clinical syndrome of radiation myelopathy is well documented (Malamud, Boldrey, Welch, and Fadell, 1954; Itabashi, Bebin, and De Jong, 1957; Dynes and Smedal, 1960; Pallis, Louis, and Morgan, 1961; Atkins and Tretter, 1966; Baldus, 1966; Hughes, 1966; Kristensson, Moulin, and Sourander, 1967; Reagan, Thomas, and Colby, 1968; Van den Brenk, Richter, and Hurley, 1968; Lehmann, Zett, and Neumeister, 1968; Locksmith and Powers, 1968; Maier, Perry, Saylor, and Sulak, 1969; Philips and Buschke, 1969; Tan and Khor, 1969; Coy, Baker, and Dolman, 1969; Eyster and Wilson, 1970). It occurs invariably as an iatrogenic lesion due to irradiation of malignant tissues in the vicinity of the spinal cord. The cervical region is the commonest part of the cord to be affected, and most reports of the pathology of radiation myelopathy have been of lesions at this site.

The type of malignancy irradiated seems to have no bearing on the subsequent development of myelopathy. The exact incidence of radiation myelopathy is not known. The factors which appear to be especially important in the development of the myelopathy are total dose, field size, and dose rate. The dose-incidence relationship has been given a mathematical description by Van den Brenk et al. (1968), who also suggest that treatment in hyperbaric oxygen increases the risk of developing radiation myelopathy. These authors published formulae and curves, from which they assert that the probability of developing radiation myelopathy may be predicted if the dosage and number of fractions of radiation received by the spinal cord are known.

The onset of the myelopathy is subacute or insidious, usually with sensory and motor disturbances in the legs. Sometimes sphincteric disturbances appear first, and occasionally pain in the neck and arms is prominent. The signs indicate involvement of the corticospinal and spinothalamic pathways especially, with weakness, spasticity, and hyperreflexia in the legs and extensor plantar responses, while sensory examination usually reveals a spinothalamic level; sparing of the posterior column modalities may be seen early. The signs and usually asymmetrical at first. The course is insidiously progressive in most cases, with death within a year of the onset of neurological signs. The cerebrospinal fluid contains no excess of cells, but the protein can be slightly elevated. Investigation should be thorough, because misdiagnosis may lead to further radiotherapy to an already damaged cord. A certain diagnosis can be made only by negative myelography. Conditions to consider in the differential diagnosis include extradural metastasis, intramedullary metastasis, necrotizing myel-
tis, cord infarction, and other unrelated compressive lesions.

There have been few necropsy descriptions of radiation myelopathy. Although more than 90 cases have been published in English since 1966, only eight spinal cords from these cases have been examined histologically (Kristensson et al., 1967; Coy et al., 1969; Philips and Buschke, 1969). Five of these were described by Kristensson et al. (1967) who had been able to find 12 cases that came to necropsy before 1966. The scantiness of pathological material is probably due to a number of factors, including failure to examine, or incomplete examination of the spinal cord; in addition, some patients die in nursing homes or hospitals for the chronically ill where there are no necropsy facilities. In the last 12 years in the Royal Adelaide Hospital, four cases of myelopathy after irradiation to the cervical region for tumors of the larynx or oropharynx have come to necropsy and form the basis of this present report.

**CASE 1**
(Path. no. 13896). In August 1959, this 57 year old woman received 6,000 r central dose to the cervical region for carcinoma of the larynx. The treatment was given with the linear accelerator at 4 meV. The fields were right and left laterals, 9 × 12 cm, extending from the base of the sphenoid bone to include the spinal cord to the level of the middle of the sixth cervical vertebra. The spinal cord would probably have received the full central dose, which was given over a period of 62 days. A total laryngectomy for a recurrence of the tumor was performed in January 1960. In June 1960 she was again treated with the linear accelerator, this time for cervical node metastasis. She received 5,200 r central dose, first to a direct field 6 × 6 cm centred at the left angle of the jaw (3,200 r), and secondly to supplementary antero-posterior and posteroanterior fields 6 × 4.5 cm extending to the right and inferiorly from the centre of the lower lip (2,000 r). This treatment probably resulted in a spinal cord dose of 4,700 r over 43 days.

Twelve months after the commencement of her first course of radiotherapy, she developed stiffness and pain in her legs, pain in her right arm and jaw, incontinence of urine, and weakness of the limbs. Examination revealed a right Horner's syndrome, a quadriplegia greater on the right side, and a spinothalamic level at T8 cord segment. Posterior column modalities were initially intact. A myelogram was normal, but the CSF protein was slightly elevated at 60 mg/100 ml. (normal less than 40 mg/100 ml.). Her neurological condition gradually deteriorated, and she died 14 weeks after the onset of her symptoms. Necropsy was performed on 5 December 1960.

**PATHOLOGY**
The immediate cause of death was hypostatic pneumonia. The spinal cord at the C4–5 level showed swelling and firmness. The spinal vertebral marrow was markedly deficient in the C4–6 region.

Histologically (Figs. 1 to 4) there was gross demyelination of the lateral and posterior columns of white matter, particularly affecting the corticospinal tracts in all sections, with involvement of the spinothalamic and spinocerebellar tracts in the cervical sections. In the upper cervical region the central parts of both posterior columns were most affected, and in the upper thoracic cord only the more medial and central fibres were demyelinated. The anterior columns were spared in most sections, and any involvement was much less severe than in the other tracts.

The right side of the cord was consistently more severely affected than the left, and on this side there was definite coagulative necrosis of the anterior horn in the cervical sections, especially in the cervical enlargement. There was chromatolysis of the anterior horn cells which was most severe in the cervical sections, but it was present in all sections, varying in degree from cell to cell in each section.

In the edge of the necrotic lesions some of the tiny intramedullary vessels contained antemortem thrombi (Fig. 5) and others showed perivascular cuffing with lymphocytes and a few polymorphonuclear...
cells. There was hyaline thickening of the walls of many of the small vessels. None of these changes were seen in the thoracic section, and there were no abnormalities of the extraspinal vessels.

In the areas of demyelination, there was oedema in the cervical sections, with degenerating axons prominent. Interstitial glial nuclei were sparse. There were only occasional macrophages to be seen. Sections of the medulla were normal.

CASE 2
(Path. no. 22157). In July 1967 this 33 year old man received 1,800 r central dose to the cervical region for carcinoma of the nasopharynx with metastases to the cervical lymph node. This was given over 22 days.
with the linear accelerator to right and left lateral fields 12 × 18·5 cm which included the spinal cord to the level of the C7 vertebral body. The energy level was 4 meV. He failed to complete the planned treatment, and was persuaded to return in January 1969 to be given another 4,500 r. This was applied to the same fields, but was given in 10 treatments in hyperbaric oxygen at 3 atmospheres absolute pressure, over 39 days. The spinal cord probably received the full central dose on both occasions.

Seven months after the completion of the second course of radiotherapy, he developed a painful neck with weakness in the right arm and leg. Examination a few weeks after the onset of these symptoms revealed a quadriparesis with a sensory level to all modalities below C5 dermatome. There was some painful restriction of neck movements. A myelogram was normal, but the CSF protein was elevated at 55 mg/100 ml. (normal less than 40 mg/100 ml.). His condition deteriorated gradually over the next ten weeks, with eventual quadriplegia and total incontinence of urine and of faeces. Necropsy was performed on 16 November 1969.

PATHOLOGY At necropsy the immediate cause of death was bilateral bronchopneumonia. Macroscopically, the meninges seemed bound to the cervical region of the cord, which was a little enlarged in all dimensions to the level of the thoracic cord. There was no evidence of extradural compression. Sections of the medulla and pons were normal.

In this case also (Figs 6 to 9) there was demyelination of the posterior columns of the upper cervical cord with the medial fibres of these funiculi affected in the lower cervical sections. The lateral columns were grossly demyelinated in the cervical sections, with coagulation and liquefaction of the central portion of the lower cervical section. Again the damage was more extensive on one side than the other. In the thoracic sections involvement of the posterior columns was mild and the pyramidal and spinocerebellar tract involvement less severe. The lumbar section showed mild demyelination of the lateral columns. Apart from some small focal areas of demyelination, the anterior columns were again spared (Fig. 9). The coagulative necrosis in the cervical sections was bilateral. The chromatolysis of the anterior horn cells was quite severe in the upper cervical sections, but in the lower cervical sections actual karyolysis was seen. The foci of oedema extended down to the lower thoracic section in this case. A few foamy macrophages were seen in the demyelinating lesions.

No extraspinal thrombosis or vasculitis was seen, and even in the areas of greatest necrosis the prevalence of thrombi in small intramedullary vessels was no greater than in case 1, where the cord damage was apparently less. Occasional vessels showed hyaline
thickening of their walls and some perivascular cuffing with lymphocytes and macrophages was present.

CASE 3
(Path. no. 22229.) In July 1968, this 59 year old woman received radiotherapy to the cervical region for a carcinoma of the oropharynx. The treatment was given with the linear accelerator at 4 meV, in hyperbaric oxygen at a pressure of 3 atmospheres absolute. The right and left lateral fields were pentagonal in shape. She received 3,150 r central dose (3,000 r cord dose approximately) over 21 days (seven treatments) to a field which included the
spinal cord from the base of the skull to the level of the T1–2 intervertebral disc. The field size was reduced and she received 1,350 r central dose (1,200 r approximately to the cord, three treatments) over 10 days to a field which included the spinal cord posterior to the bodies of C2, C3, and the upper half of C4 vertebrae. She was given a single central dose of 450 r to a field which completely missed the spinal column.

Sixteen months after completion of her radiotherapy she developed pain and weakness in the right arm and shoulder, with sphincteric symptoms. Examination revealed a severe quadripareisis, greater on the right side, with a spinothalamic level at C2 dermatome, greater on the left side. Posterior column modalities were intact when she was first examined. A myelogram revealed a partial extradural block opposite the C4–5 disc due to an osteophyte. Despite surgical decompression, her condition deteriorated over the next five weeks. Necropsy was performed on 16 December 1969.

**Pathology** The immediate cause of death was respiratory failure due to the cervical cord lesion. There was no extramedullary tumour in the spinal canal, and the spinal cord appeared macroscopically normal. The location and severity of the cord lesions are shown schematically in Fig. 10. Sections from the spinal cord were taken at six levels. The upper cervical section demonstrated coagulative necrosis. Sections from mid and lower cervical cord, mid and lower thoracic cord and lumbar cord showed demyelination of the long tracts as the major change.

There was moderate demyelination of the posterior columns at the level of the sensory decussation of the medulla, and one pyramidal tract appeared slightly smaller than the other. There was total demyelination of the cord on one side in the upper cervical region, with coagulative necrosis of the anterior horn and white matter on this side. In the mid-cervical region the posterior as well as the lateral columns were markedly and asymmetrically demyelinated. In the lower cervical region, apart from the medial edge of one gracile funiculus, one side was normally myelinated. The corticospinal tract on the other side was demyelinated. This same distribution of demyelination was seen in the thoracic and lumbar sections, with decreasing severity caudally.

In the upper cervical section, in the region of necrosis there were numerous lymphocytes in the perivascular spaces in the posterior horn (Fig. 11)
and one small haemorrhage was seen in this area. There was axonal swelling and degeneration in the demyelinated areas (Fig. 12). Glial nuclei were present in reduced numbers and there was little evidence of gitter cells. The anterior horn cells showed varying degrees of chromatolysis. There was thickening of arteriolar and venular walls and proliferation of capillaries on the more affected side. There were two flecks of arachnoidal calcification in the anterior fissure. Varying degrees of chromatolysis of the anterior horn cells was seen in the lower thoracic and lumbar cord.

Hyaline thickening was seen in only a few of the vessels of the mid-cervical and more caudal sections, but there were lacunes around many of these, a finding normally associated with hypertension. There was congestion of many vessels.

CASE 4
(Path. no. 12420.) In January 1957, this 61 year old woman received 5,000 r central dose via deep x-ray to the cervical region for a cricopharyngeal carcinoma. This was given with a Sieman's apparatus (190 kV; 17 mA; 1/2 mm Cu, 1/2 mm Al filter; focus-skin distance 50 cm) to right and left anteroposterior and posteranterior oblique fields.

The information now available is inadequate to estimate the dose which the cord must have received from the edges of these fields. In August 1957...

FIG. 10. Cases 3 (left) and 4. Diagrammatic representation of the necrosis (black) and demyelination (stippled) in the cords in these cases.

commenced treatment with the linear accelerator at 4 meV for a small recurrence of the tumour. The fields were $4 \times 4$ cm right and left laterals, and the central dose was 6,000 r over 39 days. The cord dose was possibly about 5,000 r. In June 1958 she was again treated with the linear accelerator for a suspected extradural secondary deposit. The field was directly posterior-anterior, $6 \times 12$ cm with its upper border at the level of the spine of C7 vertebra, and the cord dose was 5,760 r, given over 30 days. In October 1958, 20 mc of radon seeds were implanted in an enlarged cervical gland, giving a dose of 6,000 r at 2 cm radius, and hence a possible cord dose of 1,000 r.

Nine months after the completion of her second course of radiotherapy, she developed urinary...
symptoms, with paraesthesiae of the feet and legs. Weakness of the arms and legs developed after a further four months. Examination revealed a right Horner’s syndrome, and an asymmetrical spastic paraparesis, with a level to spinothalamic sensation at C3 dermatome, with posterior column modalities intact. Clinically, there was no evidence of recurrence of the primary tumour. A myelogram was normal and the CSF was normal (protein 25 mg/100 ml).

During the next 12 months her condition gradually deteriorated, with progression of her spinal cord signs. She also became depressed and developed postural hypotension. Necropsy was performed on 20 April 1959, 12 months after the onset of her spinal cord symptoms.

**PATHOLOGY**

The immediate cause of death was hypostatic pneumonia. The spinal cord was extremely soft over a length of 4 cm corresponding to the region of irradiation. There was no evidence of tumour in the spinal canal or vertebral bodies. There were four sections taken. The cervical section was distorted and necrotic. The mid-thoracic, lumbar, and sacral cords showed demyelination as the major pathological change.

Histologically (Fig. 10) the cervical cord was liquified, leaving only the posterior and anterior columns of white matter. The central portions of the posterior columns were demyelinated. All sections were distorted, but there was no marked demyelination of the posterior columns in other sections. The anterior columns had been spared in all sections. Both lateral columns were equally demyelinated, and in the thoracic, lumbar, and sacral sections the demyelination was more apparent in their posterior parts. The leptomeninges were thickened in the upper cervical region, and were infiltrated with lymphocytes.

In the remaining parts of the cervical cord there was coagulative necrosis of the central grey matter, and some areas of pronounced axonal swelling in the white matter. There was some hyaline thickening of small extramedullary arterioles, but no thrombosis. Perivascular gitter cells were sometimes present (Fig. 13). There was a small piece of calcium in the edge of one lateral column. There were more dark glial nuclei apparent in the grey matter than were seen in the other cases, with an increased number of thickened arterioles, some containing antemortem thrombi.

No necrosis was seen in other sections, but perivascular cuffing with lymphocytes was present in the thoracic and lumbar sections in the demyelinated areas. There was chromatolysis of varying degree in both of these sections in the anterior horn cells. There was hyaline thickening of some of the blood vessels in the latter section.

**DISCUSSION**

The pathological changes in these four cases consisted of marked asymmetrical demyelination of the lateral columns, with less striking involvement of the posterior and anterior columns. In the irradiated regions there was coagulative necrosis usually of one lateral column, although both sides were liquefied in one case. There was less involvement of the grey matter, but necrosis of the anterior horns was seen. Axonal degeneration was prominent in the demyelinated regions, with ascending and descending secondary degeneration. There was chromatolysis of the anterior horn cells, often quite remote from the cervical region. Glial and gitter cell activity was scant.

In contrast with the degree of necrosis, which did not affect all the cellular elements equally, the vascular changes were mild. There were generally vascular congestion and scattered arterioles showed hyaline thickening of their walls. Some of them also contained antemortem thrombi. There was capillary proliferation in the cervical lesions. It is most unlikely that these vascular changes could explain the magnitude of the primary necrosis, and the histology is not typical of infarction. This is in keeping with the clinical picture of the condition, which begins after a long delay and rarely in an apoplectic fashion. Moreover, the natural history of radiation myelopathy is one of insidious progression which is difficult to explain on a vascular basis.

Until recently there has been little attempt to describe the lesions of the human spinal cord in detail. Pallis et al. (1961), for example, whose paper on radiation myelitis is widely quoted, described the pathological findings of one case to be atrophy of the upper dorsal segments of the cord over a length of 4 in. in the same region as the X-ray reaction. Histological examination of the cord revealed no intramedullary metastases. The lesion was interpreted as being vascular. Reagan et al. (1968), in their report of 10 cases, described the spinal cord of one patient as showing atrophy and myelomalacia in a 5 cm segment of the cord exposed to radiation.

Although most authors attribute the patho-
logical findings to vasculitis, in one of the first detailed pathological descriptions (Malamud et al., 1954) the pathology was said to be that of acute necrotizing myelitis associated with fibrinoid degeneration of the blood vessels, and only a mild glial response. These authors commented that, although vascular changes were present, they were distinctly limited in extent when compared with the widespread disintegration of the parenchyma. Malamud repeats this observation when reporting the histology of a case described by Phillips and Buschke (1969). Coy et al. (1969) reported that the vessels characteristically, but not always, showed permeability to fibrin in the acute stages with eventual fibrosis and obliteration. They also felt that some morphologically intact vessels might be functionally defective. We were unable to confirm their observation. Kristensson et al. (1967) found pathology similar to our own and that of the other adequate descriptions in the literature, with the exception that they reported telangiectases in all of their cases. They conclude from the literature that a vascular lesion is the most important factor in the pathogenesis of radionecrosis of the spinal cord.

There has been some experimental evidence to suggest another pathogenesis. Scholz, Schlole, and Hirschberger (1960) recognized that in the spinal cords of irradiated hamsters and rabbits, the white columns are predominantly affected. This work was confirmed by Gilmore (1963). Innes and Carsten (1961) have produced a demyelinating myelomalacia in rats with radiation, and the blood vessels in their animals were normal. Marked demyelination was seen in all of our cases, while the vascular changes seen were often present well outside the region of irradiation, and could in part have been due to generalized degenerative vascular disease.

More recently Estable-Puig, Estable, Tobias, and Haymaker (1964) have shown that the myelin of rats’ brains is selectively destroyed after α-particle irradiation, a change attributed to the direct effect of radiation on myelin. Zeman (1966) considered that the effects of radiation on the murine spinal cord might be due to a delayed effect on the glial elements, which multiplied rapidly after irradiation and then died after full division, so that a delayed myelopathy occurred 200 days after irradiation. The effect on the oligodendroglia would then affect the myelin, and also explain the poor response by all types of glial cells seen in necropsied human cords.

There is little clinical, pathological, or experimental evidence to support the widely held belief that vasculitis is the primary pathological change in radiation myelopathy. Moreover, recent experimental studies suggest that direct effects of radiation on the neural elements are more likely pathogenetic factors.

We are grateful to Dr. N. D. M. Harvey, Senior Staff Radiotherapist to the Royal Adelaide Hospital, for making available the details of the treatment of these patients.

REFERENCES


