

# Delayed radiation myelopathy: Differential diagnosis with positron emission tomography/computed tomography examination

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## ABSTRACT

Myelopathy is a rare but serious complication of radiation therapy (RT). Radiation myelopathy is white matter damage to the spinal cord developed after a certain period of application of ionizing radiation. Factors such as radiation dose and time between applications affect the occurrence as well as the severity of myelopathy. In those patients, positron emission tomography/computed tomography examination has a very important role both in the diagnosis and in the differential diagnosis of lesions. In this case report, the case of progressive paraparesis, developed in a 52-year-old female patient operated with pulmonary mucinous cystadenocarcinoma diagnosis and who received chemotherapy and RT following surgery, has been reported.

**Key words:** Differential diagnosis, positron emission tomography, radiation myelopathy

## Introduction

It is well known that the spinal cord is a critical organ as it plays an enhanced radiosensitivity relative to neighboring normal organs or neoplastic tissues. Radiation myelopathy is defined as injury to the spinal cord by ionizing radiation.<sup>[1,2]</sup> Radiation myelopathy is divided into four categories according to the clinical spectrum:<sup>[1]</sup> Acute paraplegia or quadriplegia,<sup>[2]</sup> Lower motor neuron findings,<sup>[3]</sup> Acute transient radiation myelopathy, and<sup>[4]</sup> Chronic progressive radiation myelopathy (delayed radiation myelopathy; DRM). DRM is a rare but serious complication of RT.<sup>[3]</sup> It typically develops after a certain latent period and ranges from months to few years following RT. Commonly, clinical manifestation is slowly progressing ascending sensorimotor disturbance including tetraplegia or paraplegia, bowel and bladder sphincter disturbances.<sup>[2,4]</sup> For the diagnosis of DRM, the main criteria are the following:

The affected spinal cord segment must be in the irradiated zone, the symptomatology must correspond to the involved spinal cord segment, and there must be a latency period of more than six months. The differential diagnosis of DRM represents a challenging problem.<sup>[1-3]</sup> Primary or metastatic intramedullary neoplastic lesions and other neurological pathologies presenting with myelopathy must be ruled out.

## Case Report

A 52-year-old woman was admitted to our hospital with progressive onset of lower extremity weakness for two months. Neurological examination revealed spastic paraparesis (grade: 4/5), sensory deficit below the T7 level, mild hyperreflexia on lower limbs, extensor plantar responses, and clonus on the right side. In her medical history, she received RT and chemotherapy for pulmonary mucinous cystadenocarcinoma on right upper lobe two years prior to her admission. A review of the radiation treatment chart revealed the RT conducted in two phases. In the first, she had received 20 fractions of 2 Gy per month.

Two months later, a second phase RT was given in 11 fractions 2 Gy each. Total tumor dose of 62 Gy was given in three months. The 18 months subsequent to RT were uneventful.

Magnetic resonance imaging (MRI) of the spinal cord demonstrated a long segment of intramedullary lesion extending from T3 to T6 levels. The spinal cord appeared diffusely enlarged over the involved segment and a partially enhancing lesion was observed after Gadolinium administration [Figure 1]. Suspected diagnoses according to MRI findings were primary intramedullary tumor,

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metastatic tumor, or radiation myelitis. The spinal tap revealed a normal cerebrospinal fluid (CSF) chemistry and microscopy. Somatosensorial evoked potential responses were prolonged on right lower limb and absent on the left.

For positron emission tomography (PET)/computed tomography (CT) examination, the patient was intravenously injected 402.93 MBq (10.89 mCi) of F-18 fluorodeoxyglucose (F-18 FDG). After 90 minutes of uptake period, the patient was imaged using an integrated PET/CT camera (GE Discovery STE 8, USA). In the PET/CT images, there was no pathological FDG uptake suggesting malignancy at the spinal cord in the thoracic region [Figure 2]. On the basis of patient history, clinical and radiological findings, the patient was diagnosed as DRM.

The patient was treated with high dose methylprednisolone, 1 g/day for 5 days (pulse therapy) followed by oral

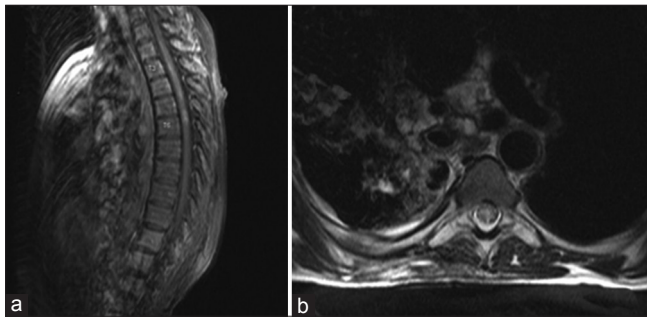
methylprednisolone 80 mg day<sup>-1</sup> for a week, tapered over 3 weeks. Simultaneously, rehabilitation therapy was also applied. Despite these therapies no objective improvement was detected on neurological examination in six months. Moreover, spasticity deteriorated slightly.

The control MRI findings were not parallel to neurological examination results. Follow-up MRI of spinal cord showed complete resolution of the hyperintense lesion on spinal cord [Figure 3].

## Discussion

Myelopathy is a rare but serious complication of RT. The first radionecrosis in the brain and the spinal cord were reported by Fisher and Holfelder in 1930 and Ahlbom in 1941. Radiation myelopathy is characterized by demyelination depending on the white matter damage caused by ionizing radiation after a certain latent period. Myelinated fibers and blood vessels are the most commonly affected structures.<sup>[1,2]</sup> Radiation dose, time between RT applications, affected spinal cord level and chemotherapy affect the occurrence and severity of myelopathy.<sup>[3-5]</sup> The thoracic segment of the spinal cord is reported to be able to tolerate 200 cGy per day up to 5000 cGy radiation.<sup>[6]</sup>

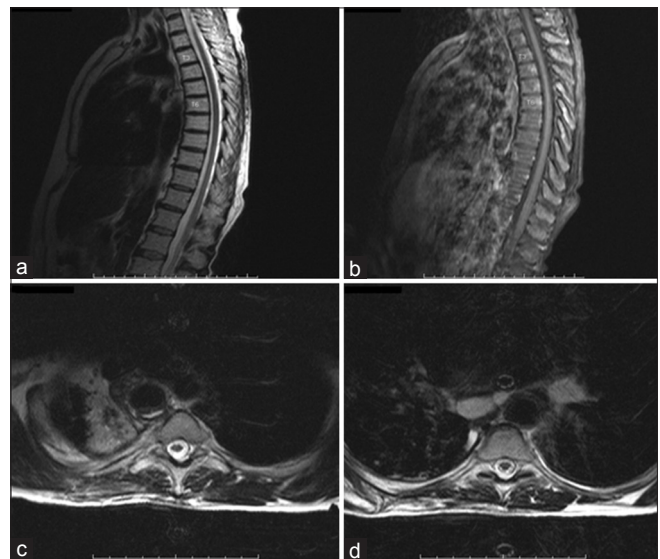
The pathogenesis of DRM is still controversial. Oligodendrocytes and endothelium have been interpreted as the major target cells of radiation myelopathy.<sup>[5]</sup> According to “glial theory”, radiation induces DNA damage in oligodendrocytes and its progenitor cells, resulting in myelin breakdown and destruction of the white matter. According to “vascular hypothesis”, vascular



**Figure 1:** Magnetic resonance imaging of spinal cord demonstrated a long segment intramedullary lesion extending from T3 to T6 levels. The spinal cord appeared diffusely enlarged over the involved segment and partially enhancing lesion was seen after Gadolinium administration. (a) T1 contrast-enhancing sequence on sagittal plane and (b) T2 sequence on axial plane at level of T5 vertebra



**Figure 2:** For positron emission tomography/computed tomography (PET/CT) examination, the patient was intravenously injected 402.93 MBq (10.89 mCi) of F-18 fluorodeoxyglucose (F-18 FDG). After 90 minutes of uptake period, the patient was imaged using an integrated PET/CT camera (GE Discovery STE 8, USA). In PET/CT images, there was no pathological FDG uptake suggesting malignancy at the spinal cord in thoracic region



**Figure 3:** The control magnetic resonance imaging findings were not parallel to neurological examination results. Follow up MRI of spinal cord showed completely resolution of the hyperintense lesion on spinal cord [Figure 3]. (a) T2 sequence on sagittal plane, (b) T1 contrast-enhancing sequence on sagittal plane, (c) T2 sequence on axial plane at level of T3 vertebra and (d) T2 sequence on axial plane at level of T6 vertebra

injury secondary to irradiation causes circulation disturbances in the spinal cord and induces white matter lesion. Experimental studies indicate that there may be radiation-induced vascular hyperpermeability and venous exudation. Also, atrophy and necrosis may also develop in the spinal cord depending on the vasculopathy.<sup>[1,2]</sup> Now, it's generally accepted that both these theories play a role in the pathogenesis of DRM.

DRM should be suspected in those patients presenting with neurological disturbances related to spinal cord pathology, after a latency period ranging from 6 to 24 months following RT. Neurological damage observed in the clinic is proportional to radiation dose received per day, the total dose and the length of spinal cord segment in the radiation field. Common clinical situation; clinical manifestations such as Brown-Sequard syndrome, tetraparesis or spastic paraplegia, sensory loss and bowel and bladder dysfunction may develop.<sup>[2,4]</sup>

Acute transient radiation myelopathy, developing after RT of the spinal cord for lymphoma and other tumors, often occurs at the end of the first year. DRM, also known as progressive radiation myelopathy, is a rare but serious complication of RT. The chronic progressive form, as the most common, occurs usually in average 9-18 months after completion of RT.<sup>[2]</sup> The total radiation dose given to our patient was 6200 cGy which is beyond the reported tolerance limits. In addition, the high proportion of fraction RT, irradiation of whole thoracic spinal cord and chemotherapy are risk factors which increase the occurrence and severity of clinical signs.<sup>[5]</sup>

The main criteria for the diagnosis of DRM have been explained as follows: The effected spinal cord segment must be in the irradiated zone; the symptomatology must correspond to the involved spinal cord segment; and there must be a latency period of more than six months. In addition, absence of spinal cord metastases or primary spinal cord lesions is required for the diagnosis.<sup>[1-3]</sup> As our patient received RT for lung mucinous cystadenocarcinoma, the thoracic spinal cord had been affected by RT. Neurological examination findings were as follows; sensory loss below the level of T7 and spastic paraparesis (grade: 4/5) in both lower extremities, mild hyperreflexia, bilateral Babinski reflexes positivity and positivity of clonus on the right side indicating signs compatible with first motor neuron injury. The level of neurological involvement is in the radiation field in our case who received spinal cord radiation.

The differential diagnosis of DRM is a challenging problem. MRI is the most widely used diagnostic method to rule out primary and metastatic intramedullary neoplastic lesions and other neurological pathologies in patients presenting with myelopathy. MRI findings may be normal in radiation myelopathy, but also hyperintensity in T2 sequences and gadolinium enhancement in T1 sequences can be observed depending on spinal cord edema.<sup>[1]</sup> Partial gadolinium enhancement and hyperintensity in T2 sequences were detected in our patient. In nerve

conduction studies, slowing or complete block may be seen in spinal conduction. CSF examination is usually normal, but mild elevation of protein level and lymphocytosis can also be seen.<sup>[3,5]</sup> In our case, CSF examination was normal. Somatosensorial evoked potential responses were prolonged on right lower limb and absent on the left.

PET/CT scans are the most important diagnostic tools for differential diagnosis of radiation myelopathy from primary spinal cord lesions and spinal metastases.<sup>[1,2,5]</sup> Fludeoxyglucose (FDG) is a glucose analog that is phosphorylated in the cells but which is not further metabolized. Most malignant tumors show increased uptake of FDG, because malignant transformation and tumor cell growth are associated with over expression of glucose transporters and increased hexokinase activity.<sup>[7]</sup> In our case, there was no pathological FDG uptake suggesting malignancy at the spinal cord in the thoracic region. However, our case was diagnosed as radiation myelopathy because of absence of pathological FDG activity in the spinal cord.

In PET studies performed in previous years, due to low spatial resolution of PET cameras, pathologic changes showing usually focal radiation necrosis of the brain (such as decreased FDG uptake and perfusion) were studied. However, very few studies were conducted on the spinal cord.<sup>[8]</sup> Normally the spinal cord has a very low FDG uptake, because of the considerable proportion of white matter with a low FDG uptake relative to small bulk of the gray matter.<sup>[9,10]</sup> Instead of a decreased FDG uptake of the spinal cord region exposed to high-dose irradiation, as expected on the basis of brain studies relating to radiation injury, we observed an increased FDG accumulation in the irradiated region. An elevated glucose metabolic rate can be a concomitant sign, with cell division or inflammatory processes. The irradiated part of the spinal cord, however, did not exhibit a higher than background methionine accumulation, providing strong evidence against a significant cell proliferation.<sup>[11]</sup>

Inflammation is an energy-demanding process, and could therefore be a reason for an increased glucose consumption. The results of pathological studies emphasized that inflammatory reaction is important in radiation myelopathy.<sup>[9,12,13]</sup> Secondly, a decreased FDG uptake of the brain following high-dose radiation may support the argument that inflammatory reactions of glial and astrocytic elements of the spinal cord would probably not cause a considerable increase in FDG accumulation.<sup>[8]</sup> Thus, the explanation of the increased glucose consumption may be based on other phenomena involving an augmented energy requirement.<sup>[12-14]</sup>

Radiation damage brings about alterations in the molecular structure of the axon membrane, demyelination being one of the most pronounced changes.<sup>[12-14]</sup> Having lost the myelin sheath, the axons display action potential conduction at a reduced speed.<sup>[15,16]</sup> The extent of the neurological deficit observed in our patient during the culmination of the

symptoms rendered a large-scale degeneration of the spinal cord probable, involving practically the entire white matter at the level of the irradiated region.

No treatment has conclusively been shown to be of value in DRM. Although some patients who benefited from corticosteroids, warfarin, pentoxifylline, vitamin E, and hyperbaric oxygen treatments were reported; no treatment was shown to affect the progressive course of neurological situation in the treatment of DRM. As damage in radiation myelopathy is irreversible, treatment is usually supportive. Some patients have derived a short-term benefit from steroids,<sup>[7]</sup> which may be related to the edema and inflammation. In our three patients, steroids did not produce a beneficial effect. Although vasoactive drugs are thought to be useful in traumatic myelopathy, this is not the case in DRM.<sup>[17]</sup> Anticoagulation showed stabilization or improvement in two studies,<sup>[18,19]</sup> but no subsequent publications are available to confirm these findings. Hyperbaric oxygen has been investigated and showed improvement of symptoms in six of the nine patients treated.<sup>[20]</sup> Mechanisms of action of steroids and hyperbaric oxygen used in the treatment of radiation myelopathy are unclear.<sup>[3]</sup> Depending on the severity of the outcome, and in view of the low risk of side-effects of these three therapies, a combination of treatments may be proposed. In our case, no positive response to steroid treatment could be achieved and improvement in clinical symptoms was observed with supporting physical therapy program.

As a result, PET/CT examination has an important role in diagnosis of radiation myelopathy and differential diagnosis from other lesions, and also is a valuable diagnostic method in planning of treatment.

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