

Radiation-induced peripheral neuropathies: etiopathogenesis, risk factors, differential diagnostics, symptoms and treatment

Ljiljana Vasić

SUMMARY

The success of radiation oncology has led to longer patient survival. This provides a greater opportunity for radiation injuries of the peripheral nerves to develop. Peripheral neuropathy in cancer patients may result from either tumor recurrence or as a consequence of radiation therapy. Distinguishing between radiation injury and cancer disease recurrence as a cause of nerve dysfunction may be difficult. In this article the etiopathogenesis of radiation-induced peripheral neuropathies has been discussed as well as main risk factors, symptoms and method of treatment.

Key words: Neoplasms; Radiotherapy; Radiation Injuries; Fibrosis Peripheral Nerves

Introduction

Neuropathy is a common finding in cancer patients. In patients with a known cancer diagnosis, efforts should be made to elucidate the etiologies of such neuropathy. The most common cause of new-onset neuropathy is progression of tumor or recurrence of such tumor (1,2). Cancer can directly cause neuropathies or indirectly result in paraneoplastic neuropathies (3,4). Signs and symptoms from neuropathies attributable to cancer can help with cancer diagnosis and contribute to disease prognosis. Neuropathies can be directly caused by oncologic treatments, including chemotherapy and radiation therapy (5-13). The goal of this review are neuropathies arising from radiation therapy.

Incidence and prevalence

The exact incidence or prevalence of radiation-induced neuropathies in cancer patients has not been well established. The current literature on this topic is sparse, consisting mostly of case reports or series. The incidence of radiation-induced neuropathies is variable, dependent on localization of radiation focus, radiation dosage and modalities of radiation delivery (14,15). For example, a case series of 739 patients in whom intraoperative radiation therapy was used reported peripheral neuropathy as the predominant toxicity in 12% of those patients (16). Another study of patients with colorectal cancer receiving intraoperative radiation reported a higher incidence of neuropathy of 23% with a higher radiation dosage (17).

Pathophysiology

To understand how radiation can induce neuropathic changes in the peripheral nerves, it is helpful to examine how ionizing radiation affects normal tissues. Radiation kills cells by causing irreversible DNA damage (18). There is a direct relationship between the amount of physical energy deposited, the degree of DNA damage, the number of cells killed and extent of tissue injury (19). In addition, other factors, including hypoxia, cytokines and cell-cell interaction, may play a role in promoting cell death or survival (20,21). Cells lethally injured by radiation energy may undergo cell death by either apoptosis or necrosis. With apoptosis, cells commit "suicide" by breaking down into apoptotic bodies and being resorbed by neighboring cells (22,23). In necrosis, cells break down into fragments, release lysosomal enzymes and generate inflammatory response. This inflammatory reaction involves release

of cytokines and inflammatory mediators. Initial nonspecific changes at tissue level can include fibrosis, atrophy, and ulceration (24,25).

Tissue response can further be broken down into two categories of early effects and late effects. Early tissue changes occur within days or weeks of irradiation treatment, while late changes can appear months or even years after radiation treatment. Early effects are often seen in tissue with cell populations that have high turnover rate that is gastrointestinal mucosa, bone marrow, skin and oropharyngeal and esophageal mucosa (26). Late radiation effects are seen typically in tissues that are nonproliferating or slowly proliferating such as oligodendroglia, Schwann cells, kidney tubules and vascular endothelium (27,28). Pathogenesis of late effects involves necrotic cell death, production of proinflammatory and profibrotic cytokines and alteration of gene expression in local cells (29).

In the past, based on experimental studies, peripheral nerves were said to be relatively radioresistant due to their protected position, low metabolic rate, and low reproductive capabilities.(30,31) However, the follow-up time was very short and it is possible that radiation injures did not have an opportunity to developed (30). The early effects occurring two days after irradiation of the peripheral nerves include: bioelectrical alterations, enzyme changes, abnormal microtubule assembly and altered vascular permeability (30,32). Two phases of neuropathy following irradiation were described by Mendes and co-workers. The first phase includes changes in electrophysiology and histochemistry. The second, later phase is connected with fibrosis of the tissue surrounding the nerves (32). Such fibrosis with subsequent compression of nerve bundles is suspected to be suspected to be primary etiology of peripheral neuropathies (16).

The peripheral nerves consist of axon bundles. Thus, the axons of nerve cells are likely affected by radiation to the peripheral nerve. But the axons are supported by myelinated sheaths of Schwann cells as well as local blood vessels. These supporting cells are more vulnerable to the ionizing irradiation. Late effects can include myelin destruction, degenerative changes of Schwann cells and vascular changes, such as endothelial cell loss, capillary occlusion, degeneration and hemorrhagic exudates.

CLINICAL PRESENTATION

Patients with neuropathies can present with many different signs and symptoms, depending on the nerves affected. With radiation delivered close to spinal cord where the nerve roots emerge, the patient may experience radiculopathies. At the level of cervical and lumbar spine, the patient often complains of back pain, headaches, extremity pain, numbness, paresthesia

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University of Kragujevac Medical Center,
Department of Oncology, Kragujevac,
Serbia

Correspondence to:

Mr sci dr Ljiljana Vasić, Bukureška 13,
34000 Kragujevac, Serbia

E-mail: ljiljana76@eunet.yu

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and weakness. Radiation to the thoracic area may cause noncardiac chest pain and abdominal pain (33-35).

With radiation therapy for breast cancer, lung cancer and Hodgkin's lymphoma the patient receives ionizing irradiation to the superior thorax covering the brachial plexus anatomic location.(2,36,37,38) Radiation-induced brachial plexopathy may be due to radiation damage of the nerve or due to compression of the nerve fibers by fibrosis of the supraclavicular and axillary connective tissue (39,40). The fibrous connective tissue becomes more permanent, dense and inelastic (41). The incidence of brachial plexopathy increases with the time after radiation (8,13). The evolution of fibrosis is a slow process (15). The median interval between radiotherapy and occurrence of brachial neuropathy has been reported to be 1-4 years (15,41-43), but also some neuropathies have occurred many years after completion of radiation treatment (from 6 to 22 years) (39,40,44,45). Early onset of brachial plexopathy during radiotherapy or 1-2 months after its completion has been observed by some authors (45-48). Abnormal radiosensitivity of genetic origin was suggested as a possible cause of acute onset of brachial plexopathy occurring after only a few fractions (46). Gerard and co-workers described acute ischemic brachial plexus neuropathy due to occlusion of the subclavian artery during radiotherapy (47).

However, typical radiation-induced brachial plexus neuropathies occur after a latent period in patients with the following risk factors: high radiation doses, overlapping fields, increased dose in axilla due a smaller separation at that point and concurrent chemotherapy (40,49). The risk of brachial plexus damage was shown to increase with total radiation dose and dose per fraction (43,50). The total tolerance dose for brachial plexus was suggested by Emami to be 60 Gy (19). This observation was confirmed by Bajrovic and co-workers (51). However, brachial plexus neuropathy was observed also after radiotherapy to a dose of 40 Gy in 20 fractions (35-37,40,45). The incidence of brachial plexus injury significantly increased with doses greater than 2 Gy per fraction (30).

With brachial plexopathy, the patient experiences chronic neuropathic of the affected extremity and also limb paralysis in severe cases (52). If radiation is closer to the proximal brachial plexus, the patient exhibits characteristic cervical radiculopathy (10). Any nerve root in the cervical region can be affected, but most commonly the C5, C6, C7 and C8 nerve roots are involved in cervical neuropathies with related clinical signs and symptoms.

Assessment

Most common neuropathies in cancer patients can be resulting from direct tumor growth and proliferation. That is why patients with known cancer diagnosis presenting with new onset of pain or significant increase in severity of pain should be vigilantly worked up for tumor progression. A complete history and physical examination is the first essential step. The clinical interview should be focused on questions about onset, duration, progression and nature of neuropathic symptoms such as pain, numbness and weakness. The physical examination is focused on the site of complaint and also the whole body to rule out other possible noncancer etiologies for neuropathies.

A thorough diagnostic workup of the neuropathies is essential in eliciting the etiology and possible mechanism of neuropathic pain. This includes laboratory, imaging and functional neurophysiologic studies. Laboratory workup may include complete blood count, fasting blood glucose, sedimentation rate,

general chemistry profile, thyroid function tests, vitamin B12 and folate levels, hepatitis viral tests, antinuclear antibodies and rheumatoid factor. Imaging studies, including plain radiographs, computed tomography (CT) scan and magnetic resonance imaging (MRI) scan are valuable to determine any tumor involvement of the neurological structures or postchemotherapy and radiation changes of surrounding tissues. CT was the first useful radiographic study which was able to show masses of the recurrent tumor (43,55). Now, MRI is the technique of choice to distinguish tumor relapse from injury after radiotherapy (39,45,46). Radiation fibrosis may have both low and high signal intensities on T2-weighted images (45,54). In some cases the diagnosis may be clarified with an ultrasonographic examination (44). Certain diagnosis is based on histopathological (HP) examination. The material may be obtained by needle biopsies or by excision of the soft tissue near the brachial plexus during surgical exploration (10). The result of the HP examination allowed the ultimate differential diagnostics between the possibility of malignant infiltration and radiation-induced fibrosis to be performed. Additional studies including electromyographic (EMG) findings to evaluate the functional integrity of the affected muscle groups and relevant nerve function. The EMG findings in radiation-induced neuropathy may include: reduction in amplitude, slowing of conduction velocity and increases in latency (40,41,46). Currently, EMG does not play an important role in discrimination between neoplastic and radiation-induced neuropathy (46,55).

The next scale is used to assess various grades of late effects after radiation therapy: grade 1 - mild sensory deficits, no pain; grade 2 - moderate sensory deficits, tolerable pain, mild weakness; grade 3 - continuous paresthesia with incomplete motor paresis, pain medication required; grade 4 - complete motor paresis, excruciating pain, muscle atrophy. Radiation-induced neuropathies are found to be a progressive process (52).

The prevention of radiation-induced neuropathies is a difficult challenge. The aggressiveness of therapy must be balanced against the risk of recurrence. The reduction of radiation field size and total dose were proposed do decrease the risk of late complication after radiotherapy (30). However, the success of radiotherapy depends on the total radiation dose and it is impossible to predict the late complications of this treatment. The treatment of radiation-induced neuropathies depends on the grade of severity of injury. In grades 1 and 2 conservative treatment is required which includes non-narcotic and narcotic analgesics and anesthetic interventions (30,46,52). Surgical exploration is fully justified in grades 3 and 4 (30,44,45).

Conclusion

Peripheral neuropathies are unfavorable consequences of cancer treatment. Although not yet fully understood, the pathophysiology of radiation-induced peripheral neuropathies involves the late effects of radiation on the peripheral nerves and surrounding tissues.

Subsequent tissue changes result in inflammation and fibrosis that affect the peripheral nerve and lead to peripheral neuropathies. In cancer patients with new neuropathies a complete diagnostic workup is recommended to rule out other etiologies, such as progression or metastasis of cancer. Treatment of such peripheral neuropathies requires a multimodality approach, including medications and supportive therapy.

Conflict of interest

We declare no conflict of interest.

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address: Vinča Institute of Nuclear Sciences, P.O. Box 522, 11001 Belgrade, Serbia

phone/fax: 0381 11 244 74 57

e-mail: nss@vin.bg.ac.yu

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