

CASE REPORT

RADIATION-INDUCED OBTURATOR NERVE INJURY IN CERVICAL CANCER

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Cancer itself can have lifelong devastating effects, but radiation treatment can often also result in long-lasting neurological and musculoskeletal complications, leading to subsequent severe functional impairments. Physiatrists caring for the cancer rehabilitation population must be able to recognize and treat radiation-induced peripheral nerve injuries. This report presents a rare case of radiation-induced obturator neuropathy in a patient with recurrent cervical cancer.

Key words: cancer rehabilitation; obturator nerve injury; radiation induced peripheral neuropathy.

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Cervical cancer is among the most common cancers in women. In the USA, invasive cervical cancer is diagnosed in close to 14,000 women annually (1). The standard of care for treatment of locally advanced cervical cancer includes the combination of external beam radiation therapy and brachytherapy, a local source of radiation placed directly into or next to the tumor site, with concurrent chemotherapy (1). While radiation proves effective in eliminating radiosensitive tumours, it simultaneously risks radiation exposure of healthy tissue surrounding the cancerous cells. Injuries can present differently based on the chronicity of the symptoms, including acute transient and delayed progressive forms. Studies show that, in the transient form, symptoms can worsen over some months, then stabilize, prior to completely regressing (2).

Radiation-induced peripheral neuropathies (RIPN) are a known complication in patients receiving radiotherapy. Radiation damage to the nerve is believed to be caused

LAY ABSTRACT

The number of cancer survivors is increasing annually. Many of these survivors will have received some form of radiation therapy. Whether their last dose was 6 months or 20 years ago, radiation can cause injury to nerves and muscles at any point after treatment. If physicians do not recognize these complications at an early stage, radiation injuries can result in progressive pain and functional impairments that can be lifelong. We report here a rare case of nerve injury in a patient following radiation, emphasizing the key findings of presentation and the testing and management needed in order to prevent long-term pain and improve overall quality of life in cancer survivors.

by an initial microvascular injury, leading to delayed nerve injury through radiation-induced fibrosis, ultimately leading to RIPN. Symptoms can be progressive in nature, and typically occur years after initially receiving treatment, with the nerve involvement consistent with the location of radiotherapy delivered (3). The pathogenesis behind RIPN is thought to be three-fold: the first phase involves chronic local inflammation, which leads to the second phase with over-activation of fibroblasts and myofibroblasts causing significant active fibrosis via transforming growth factor beta 1 (TGFβ1) protein. The third phase, or the late fibrotic-atrophic phase, causes loss of parenchymal cells and compromises the vascularity of the capillaries (3). This process ultimately causes direct axonal injury and demyelination, extensive fibrosis within and surrounding nerve trunks, as well as ischemia to the vessels supplying the nerves (4).

RIPN is dose-dependent and can be amplified with concomitant chemotherapy and/or lymph node dissection. Total radiation doses estimated as around 50–60 gray (Gy) have been associated with a higher risk of developing

RIPN. However, there is large variability among radiation doses causing long-term effects (5). In cervical cancer, the rate of RIPN to the lumbosacral plexus is reported to occur in 1.3–6.7% of patients receiving radiotherapy to the pelvis (6). The clinical presentation of RIPN may vary, typically presenting in 1 or both lower limbs and including numbness, paraesthesia, weakness, and even paralysis. Urinary and faecal incontinence has also been noted (6). Furthermore, presentation will depend on the specific nerve involvement, based on the location of radiotherapy. The obturator nerve is derived from the lumbar plexus and exits the pelvis through the obturator foramen; it innervates muscles involved in thigh adduction, as well as providing sensation to the medial thigh via a small cutaneous branch.

We report here a case of a young patient with cervical cancer who developed RIPN of the obturator nerve, and the pathophysiology and treatment of delayed radiation neuropathy. To our knowledge, to date, there has been no published literature on RIPN of the obturator nerve.

CASE REPORT

In 2011, a previously healthy 30-year-old woman was diagnosed with cervical carcinoma stage 1B1, based on the International Federation of Gynecology and Obstetrics (FIGO) staging system, and underwent robotic trachelectomy and lymph node dissection. This staging indicates that the lesions are clinically visible, but no larger than 4 cm. The risk of metastasis to lymph nodes in the pelvic or para-aortic region is 10–22% in FIGO stage 1B1 (7). In 2014, biopsy revealed recurrent disease in the left para-aortic lymph nodes, and the patient underwent proton therapy (45 Gy to the whole pelvis, para-aortic lymph nodes; 18 Gy boost to recurrence site) with concomitant cisplatin chemotherapy, then 4 cycles of carboplatin/taxol. In 2015, the patient had a recurrence in the vaginal cuff and underwent 2 treatments of low-dose brachytherapy. Approximately 3 years later, she developed shooting pain and numbness in her left leg from her hip radiating down to her foot. At this time, her primary care physician referred her to physical therapy for sciatica. Due to vaginal bleeding at the time, a magnetic resonance imaging (MRI) of the pelvis and positron emission tomography–computed tomography (PET/CT) were also ordered and showed cancer recurrence at the left external iliac lymph node. In October 2018, she underwent stereotactic body radiation therapy (40 Gy) and began 6 cycles of carboplatin/taxol. Her left leg symptoms remained unchanged despite physical therapy and naproxen. In April 2019, she presented to her primary care provider with new-onset weakness of the left leg. An MRI of the lumbar spine did not show neural foraminal stenosis, central canal narrowing, or malignancy. Fatty replacement of the L3 to sacral bone marrow, related to prior radiation treatment, was noted. Weakness of the left leg persisted, and the patient was referred to a cancer physiatrist in August 2019. At that time, she was no longer experiencing pain distal to the

knee and only felt burning and aching pain in the thigh. On examination, no atrophy was noted in the lower extremity musculature. Based on standardized manual muscle testing, her strength was 4/5 in left hip flexion and 3/5 in hip adduction. The remaining lower extremity strength examination was 5/5. There was decreased sensation to light touch at the proximal medial thigh, but vibratory sense was preserved. She was normoreflexic with a normal downgoing plantar response. Focused examination of the left lower extremity demonstrated normal passive range of motion. Examinations testing for hip joint pathology were negative. Slump test and straight-leg raise, assessing for radicular pain, were also negative. Electromyography and nerve conduction study (EMG/NCS) of the left lower extremity was conducted. L2 through S1 myotomes were sampled on needle EMG and included muscles innervated by the femoral, obturator, sciatic, superior gluteal, and peroneal nerves. Only the left adductor longus, innervated by the obturator nerve, demonstrated abnormal spontaneous activity, with 3+ fibrillations and 3+ positive sharp waves. There was reduced recruitment and no chronic neurogenic motor unit changes. No myokymia was seen. Other muscles with L2–4 nerve root innervation, including mid-lumbar paraspinals, were normal. MRI of the pelvis with and without contrast (**Fig. 1**) revealed findings consistent with post-radiation changes and left obturator neuropathy, which were also consistent with the EMG findings.

The patient was treated with pentoxifylline, 400 mg orally twice daily, and vitamin E, 400 units orally twice daily, with the goal of reducing post-radiation fibrosis. She performed a home exercise programme with focused adductor strengthening exercises. At a 3-month follow-up,

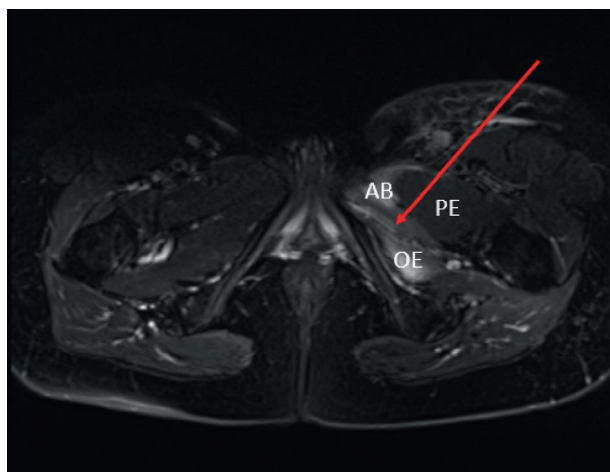


Fig. 1. Magnetic resonance imaging (MRI) lumbar plexus fat suppressed T2-weighted axial image, showing thickening of the left obturator nerve (red arrow) from the level of S1 as it courses medially along the psoas major muscle and between the pectineus (PE) and adductor brevis (AB), consistent with left obturator neuropathy. Post-radiation injury to the nerve appears hyperintense, diffuse, with uniform swelling on a T2-weighted image (7). Edema and mild enhancement of the left adductor compartment and obturator externus (OE) is present, consistent with post-radiation changes and denervation secondary to left obturator neuropathy.

the pain had completely resolved and her left hip adduction strength had improved to 4/5. She was functionally able to play soccer with friends and reported that her leg was less easily fatigued. In addition to soccer several times a month, she began aerobic exercises 4–5 times a week. Her medial thigh numbness resolved, and she reported no pain or discomfort, but would sometimes feel a slight strain on her medial thigh when abducting the left hip. She remains on pentoxifylline, vitamin E and strengthening exercises, including static hip adductor strengthening with a pillow between her knees and hip adductor strengthening while side-lying and standing.

DISCUSSION

This case discusses a rare presentation of radiation therapy-induced obturator nerve injury in cervical cancer. To help distinguish radiation-induced fibrosis from a recurrent tumour, MRI is an appropriate initial non-invasive modality (8). MRI of the lumbar plexus with and without contrast is the most accurate imaging method to determine whether a mass is intrinsic or extrinsic to a nerve of the plexus, tumoral involvement of the plexus, recurrent tumors, or post-radiation injury (9). In this case, MRI findings revealed post-radiation changes and denervation secondary to left obturator neuropathy. The diffuse spontaneous activity seen on needle EMG of the adductor longus with reduced recruitment and no motor unit morphology changes suggested an acute neurogenic injury. Only an obturator nerve-innervated muscle was abnormal. Though myokymia, or spontaneous bursts of motor unit discharges that typically occur at regular intervals, is pathognomonic for radiation-induced nerve injury, it is estimated to occur in about 60% of cases and was not seen on needle sampling in this case (7).

The radiological and electrodiagnostic findings were in keeping with the clinical findings of pain in the proximal leg, weakness of hip adduction and flexion, and medial thigh numbness. Imaging also found a partial thickness tear of the adductor longus, which probably contributed to pain and weakness of her left lower extremity. It is important to note that this patient also received a lymph node dissection, which probably contributed to her presenting symptoms, as nerve injury can be exacerbated due to compression from postoperative fibrosis or scarring (3). Furthermore, the patient also received several cycles of concurrent chemotherapy, which also increases one's risk of developing RIPN (4). As previously mentioned, there is published data on the presumed threshold for doses above which RIPN should be suspected, but significant variability among doses exists; furthermore, limited data are available on radiation doses resulting in neuropathy of specific nerves, as seen in this case. Given the chronicity of presenting symptoms and the patient's improvement in strength and resolution of pain, this case likely presents an acute transient form of radiation-induced peripheral

neuropathy. It is important to also note that when the patient presented to primary care in 2018, prior to stereotactic radiation, imaging was performed to assess for cancer recurrence and tumor compression, which would account for her left leg symptoms. In 2019, after stereotactic radiation and when she presented again with left leg symptoms, imaging was also completed in part to ensure no recurrence of cancer.

Management of RIPN is aimed primarily at symptomatic relief. Pain management may involve the use of non-opioid analgesics, such as gabapentinoids, tricyclic antidepressants, and serotonin-norepinephrine reuptake inhibitors, used to treat neuropathic pain (7). Patients should be educated on avoiding risk factors for further nerve injury, such as smoking, alcohol abuse, and uncontrolled diabetes. Physical therapy should not only include strengthening, but also compensatory strategies in the setting of loss of function and protective strategies to avoid unnecessary stretch and traction on injured areas. Further local trauma in the irradiated area should be avoided (4).

Currently, there are ongoing studies reviewing neurological outcomes in patients with RIPN receiving combined clodronate, pentoxifylline, and vitamin E (PENTOCLO) therapy (4). Pentoxifylline is a methylxanthine derivative, altering fibroblast and collagen activity. Radiation-induced fibrosis prompts myofibroblasts to create a positive feedback loop with TGF β 1; pentoxifylline breaks this cycle by inhibiting the TGF β 1 feedback cascade (10). The addition of clodronate, a bisphosphonate, inhibits osteoclastic bone destruction with anti-inflammatory effects, and inhibits macrophagic myelin nerve destruction (4). Delanian et al. performed a double-blind study in patients with breast cancer who received prior radiation therapy, which showed a significant reduction in the volume of fibrotic tissue at 6 months in patients treated with pentoxifylline and vitamin E (11). Based on these results, Jacobson et al. conducted a phase 3 randomized clinical trial with women who received prior whole-breast irradiation who were treated with pentoxifylline and vitamin E. A tissue compliance meter was used to objectively measure changes in breast tissue compliance relative to the untreated breast. At the end of 6 months, breast tissue compliance was better in patients treated with pentoxifylline and vitamin E compared with placebo (12). These studies have proven the combination of pentoxifylline-vitamin E clinically efficacious in preventing fibrosis. An alternative option is microsurgical neurolysis, which can be considered when progressive motor weakness is present and conservative modalities have failed. This method allows for nerve decompression caused by radiation fibrosis; moreover, a vascularized flap coverage restores some degree of function to the affected limb, restores blood supply to the irradiated areas, and decreases the risk of recurrent fibrosis (13). There is limited evidence to support the use of anticoagulant therapy or hyperbaric oxygen in the treatment of RIPN (7).

CONCLUSION

As the survival rate among patients with gynecologic malignancies increases, early diagnosis and understanding of long-term radiation effects is imperative in order to limit the development of irreversible complications. Given the variability in time of onset to recovery with radiation-induced complications, patients' cancer and treatment histories should be carefully gathered by the discerning physiatrist to provide appropriate diagnosis and treatment, with the aim of improving patients' overall function and quality of life.

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