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Delayed-onset lumbosacral polyradiculitis following proton precision beam therapy for localized prostate cancer: A case report

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ABSTRACT

Introduction: In males, prostate cancer is the second most diagnosed cancer worldwide and the sixth leading cause of cancer death. Radiation therapy is a common treatment modality for prostate cancer but carries a multitude of adverse effects, ranging from radiation cystitis to post-radiation neuropathy. Proton beam therapy has gained attention as a valuable alternative, due to its improved precision with targeted dose delivery and reduced toxicity. However, the risk for radiation-induced complications, such as radiation-induced lumbar radiculopathy, is not fully understood and requires further investigation.

Case presentation: We present a 68-year-old man with delayed-onset lumbosacral polyradiculitis following proton precision beam therapy for localized prostate cancer. The patient underwent proton therapy treatment for the prostate and seminal vesicles with favorable results and tumor remission. However, five months after completing radiation therapy, the patient presented with chronic lower extremity pain, weakness, and bilateral lower extremity paresthesias. MRI showed diffuse hyperintensity of bilateral L5–S3 nerve roots and an intramuscular edema-like signal involving the bilateral obturator externus and internus muscles, likely due to radiation. Additionally, EMG findings suggested the presence of chronic bilateral L5 radiculopathy.

Conclusion: The clinical manifestation of delayed-onset radiation-induced lumbosacral plexopathy is a rare and uncommon complication of external beam radiation therapy that presents as radicular or myelopathic symptoms based on the location and severity of the inflammation. This case highlights the need for continued follow-up post-radiation and emphasizes the need for a comprehensive review of the oncological history of cancer patients.

1. Introduction

Prostate cancer remains the second most common cancer diagnosed worldwide and the sixth leading cause of cancer death in males [1]. Radiation therapy is a common treatment modality for prostate cancer but comes with adverse effects such as radiation cystitis, erectile dysfunction, fatigue, bone fragility, damage to surrounding structures leading to chronic myopathies or neuropathies, and an increased risk of developing secondary malignancies [2]. Proton beam therapy (PBT) has gained attention as an alternative to conventional photon-based external beam radiation therapy (EBRT) due to its potential advantages in dose distribution and reduced toxicity [3]. PBT is a form of EBRT that uses protons instead of photons to deliver a highly conformal radiation dose to the tumor while sparing the surrounding healthy tissue. This is achieved through the unique physical properties of protons, including a well-defined range and a rapid dose fall-off beyond the Bragg peak [3,4].

The long-term effects of radiation-induced complications, such as neuropathy, are not fully understood and require further investigation [5]. This case report aims to highlight the potential for radiation-induced neuropathy as a complication of PBT for prostate cancer treatment and emphasize the importance of continued follow-up and a comprehensive review of the oncological history of cancer patients.

2. Case report

A 68-year-old male was diagnosed with intermediate-risk, biopsy-confirmed prostate cancer localized to the prostate gland (cT1b). The patient had an elevated prostate-specific antigen (PSA) level of 7.79 ng/

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Abbreviations

CcGE	Cobalt Gray Equivalent
EBRT	External Beam Radiation Therapy
EMG	Electromyography
IMPT-SFO	Intensity-Modulated Proton Therapy with Spot-Scanning and Field Optimization
MRI	Magnetic Resonance Imaging
PBT	Proton Beam Therapy
PSA	Prostate-Specific Antigen
PUFA	Polyunsaturated Fatty Acid
RT	Radiation Therapy
RILP	Radiation-Induced Lumbar Plexopathy
SV	Seminal Vesicles

mL, and the biopsy revealed a Gleason score of 3 + 4=7 (Grade Group 2) and perineural invasion. The patient did not undergo androgen deprivation therapy.

The patient received radiation therapy (RT) in two separate areas, the Prostate Seminal Vesicles (SV) and Adapt Prostate SV, using intensity-modulated proton therapy with spot-scanning and field optimization (IMPT-SFO IG Proton Plan 0.0). Over 30 days, the patient underwent 21 daily treatments for the Prostate SV area, with a dose of 243 CcGE per treatment delivered to the 0.0 Plan line. The total prescribed dose was 5250 CcGE, while the actual dose received was 5119 CcGE. In the Adapt Prostate SV area, the patient completed seven daily treatments over nine days, with each treatment consisting of a dose of 249 CcGE delivered to the 0.0 Plan line. The total prescribed dose for this area was 1750 CcGE, and the actual dose received was 1748 CcGE.

Over a 39-day period, the patient underwent a total of 28 RT treatments, with an overall dose of 6867 CcGE. Consequently, the patient experienced diminished sexual function, scoring 13/35 on the International Prostate Symptom Score and 3/25 on the Sexual Health Inventory. Additionally, the patient's bowel, urinary incontinence, irritative/obstructive, sexual, and hormone scores were 87, 66, 81, 79, and 70, respectively, indicating the impact of the treatment on his quality of life and daily activities.

Five months following the treatment, the patient developed pain in his bilateral lower extremities, along with paresthesias radiating down to his toes. This pain was predominantly triggered by walking and alleviated during periods of rest. On the day of the clinic visit, the severity of the pain was rated 4/10. Additionally, the patient demonstrated bilateral lower extremity weakness on examination.

MRI of the lumbar spine revealed multilevel degenerative disc disease, facet arthropathy, the absence of high-grade spinal canal or neural foraminal stenosis. Importantly, the MRI, performed with and without contrast displated elevated hyperintensity of the bilateral L5-S3 nerve roots. This elevated T2 signal was noted without any intrinsic enhancement/mass, indicating a lack of malignancy, or extrinsic compression. These observations pointed towards radiation-related plexopathy (Fig. 1). Furthermore, the MRI highlighted a mild fascial and intramuscular edema-like signal in the bilateral obturator externus and internus muscles, which is consistent with radiation-induced myopathy (Fig. 2).

In addition to the MRI, needle electromyography (EMG) testing was performed, which revealed normal conduction in both the motor and sensory components. Needle EMG demonstrated increased polyphasic motor units in a bilateral L5 distribution, present both proximally and distally. These findings suggested chronic bilateral L5 radiculopathy, notably more pronounced on the right side. However, due to an unremarkable paraspinal examination, a plexus-level lesion could not be definitively excluded.

After three months of unsuccessful neuropathic pain management,

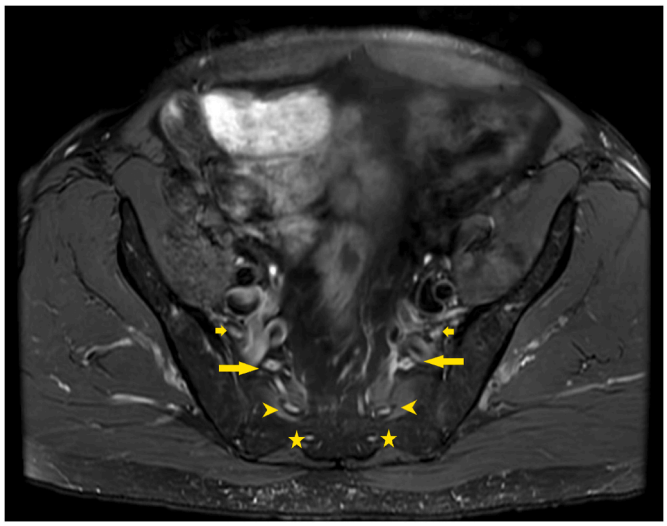

Fig. 1. MRI of the lumbar spine (with and without contrast) illustrating elevated T2 hyperintensity in the bilateral L5–S3 nerve roots. Short arrows indicate L5, long arrows point to S1, arrowheads denote S2, and stars mark S3. Findings are suggestive of radiation-related plexopathy.

which included physical therapy for pain reduction and strengthening, acetaminophen, NSAIDs, and an initial dose of gabapentin, the patient was introduced to icosapent ethyl, an agent with potential anti-inflammatory properties., the patient was introduced to icosapent ethyl, an agent with potential anti-inflammatory properties. At 3-month follow-up, the patient reported no significant change in pain severity, maintaining a score of 4/10, and showed no new focal weakness, sensory changes, or bowel/bladder dysfunction. Physical examination revealed bilateral hip flexion strength of 4+/5, with full strength (5/5) in knee movements, ankle dorsiflexion, plantarflexion, and extensor hallucis longus. Reflexes were symmetric at the patella (2+ bilaterally). The Achilles reflex was notably absent, a phenomenon sometimes observed with advancing age and not solely indicative of neuropathic involvement. This finding was correlated with age-related decline, rather than the sequelae of radiation. Light touch was intact in both lower extremities, and tenderness was noted on the paraspinal muscles and at the sacroiliac joint. Treatment recommendations included continuation of Vascepa (icosapent ethyl) at 1 g twice daily, upscaling the dose of gabapentin to 300 mg at bedtime, a Medrol dose pack, and physical therapy for strengthening.

To summarize, the patient experienced delayed-onset lumbosacral polyradiculitis as a result of proton precision beam therapy for prostate cancer. This case is unique due to the prolonged duration of the patient's symptoms and the involvement of the lumbosacral plexus. While radiation-induced lumbosacral plexopathy (RILP) is recognized as a potential complication following pelvic radiotherapy, it is relatively infrequent, with its incidence ranging from 0.3% to 1.3% [6]. This emphasizes the rarity of such cases, but it's imperative to note its occurrence and the significance of early diagnosis and intervention.

3. Discussion

The long-term outcomes of proton therapy for localized prostate cancer have been studied, and results have shown it to be favorable for high- and very-high-risk patients, with significantly lower rates of late side effects compared to other EBRTs [3]. However, as with any RT, complications can arise, and appropriate management is essential [2]. In particular, radiation-induced neuropathy in cancer survivors is a well-documented phenomenon that can manifest in various forms, including lumbosacral plexopathy [5]. In addition, although global patterns in prostate cancer incidence and mortality rates have shown a

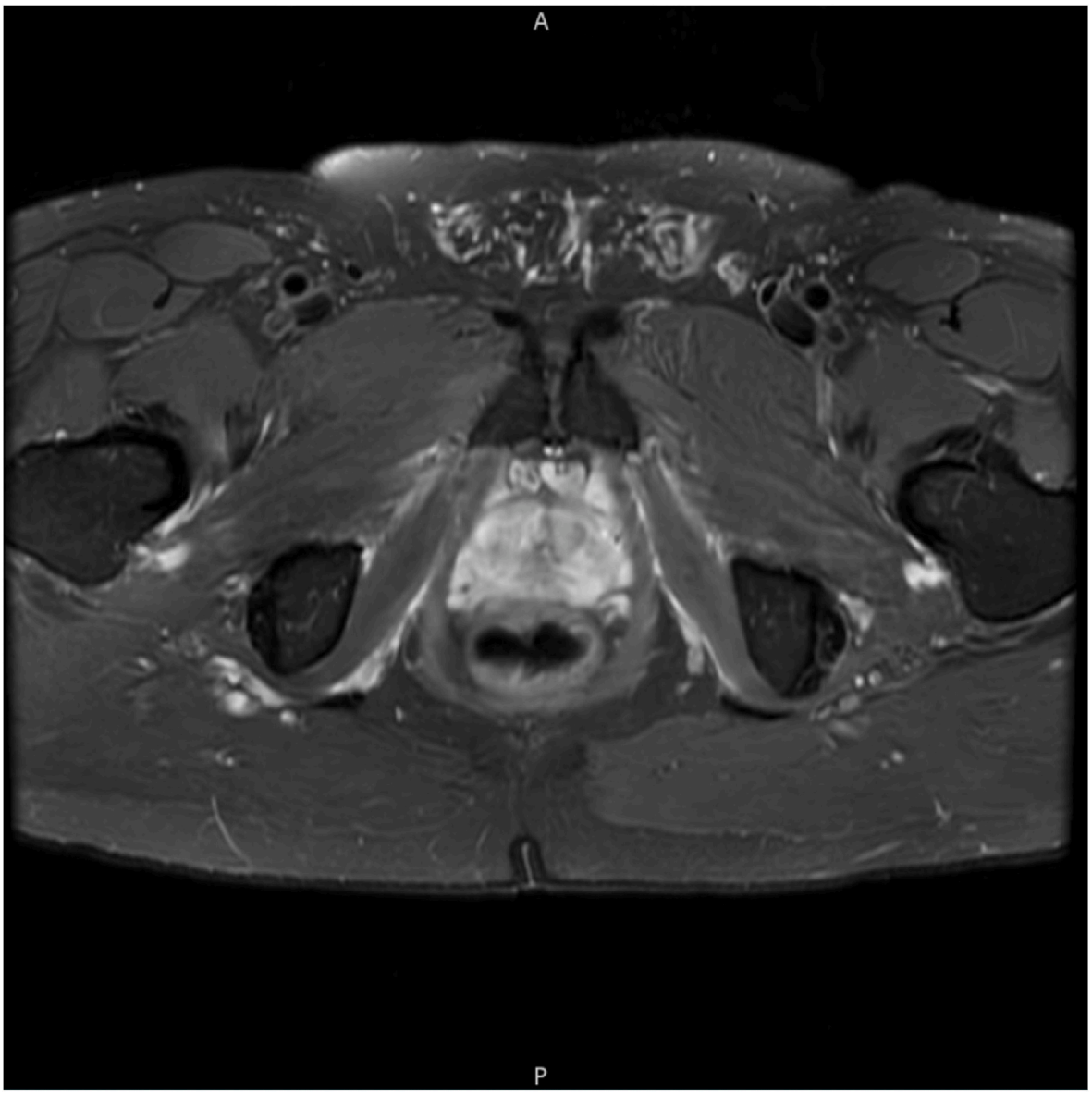

Fig. 2. MRI revealing an edema-like signal involving the bilateral obturator externus and internus muscles, likely due to radiation therapy.

general decrease, the increasing use of RT in the management of prostate cancer is likely to contribute to the prevalence of radiation-induced complications [1].

PBT, in particular, has been the subject of controversy regarding its use for localized prostate cancer [4]. Although studies have shown that it can be an effective treatment option, there are concerns regarding its cost-effectiveness and the potential for increased rates of secondary cancers compared to traditional RT [4].

Lumbosacral plexopathy is a rare but recognized complication of RT, including proton therapy. Symptoms can range from mild to severe and may be immediate or delayed in onset [7]. Though the pathogenesis of radiation-induced lumbar plexopathy (RILP) is not well understood, radiation-induced damage to nerve cells contributes to both early and late manifestations. Early changes are typically characterized by bioelectrical abnormalities, altered vascular permeability, and aberrant nerve conduction. Late changes are characterized by fibrosis of the supporting nerve tissue, with fibrotic structures even compressing the nerves [8]. In addition, evidence suggests that radiation-induced neuropathy may be mediated by inflammation and oxidative stress, which can lead to the production of reactive oxygen species and pro-inflammatory cytokines [5].

The importance of early detection of RILP cannot be understated. Once RILP is identified, specific interventions such as prompt physiotherapy, pain management strategies like the use of anti-inflammatory agents and gabapentinoids, and the initiation of omega-3 polyunsaturated fatty acid supplements can be commenced. Early intervention not only helps manage the immediate symptoms but also works to prevent the cascade of biochemical and inflammatory reactions that lead to fibrosis – the primary cause of long-term complications in RILP [8]. Additionally, early detection provides an avenue to reduce the risk of misdiagnoses, leading to more timely and appropriate care.

Various factors contribute to the risk of developing radiation-induced neuropathy, including the cumulative radiation dose, fraction size, irradiated volume, and use of concurrent chemotherapy [7]. In this case, the patient received a total cumulative dose of 6867 CcGE, which falls within the range reported in previous studies of proton therapy for prostate cancer [3,4]. However, it is important to note that the risk of radiation-induced complications is not entirely predictable and can vary widely among individuals.

The diagnosis of RILP necessitates meticulous history-taking and

physical examination. As it is a diagnosis of exclusion, it is vital to eliminate other potential pathologies, such as tumor-induced compression, infectious processes, and spondylogenic disorders [8]. Typically, the workup encompasses nerve conduction studies, EMG, cerebrospinal fluid analyses, and an MRI of the lumbar spine [7]. To affirm the diagnosis of RILP, patients must meet the following criteria: 1) there is a history of radiotherapy in the region of the plexus; 2) the primary neurologic lesion is confined to the radiotherapy-exposed segments; and 3) metastatic and other plexus disorders have been excluded [8].

In the initial stages, patients present with motor dysfunction, typically characterized by weakness with a bilateral asymmetric presentation that gradually evolves to include sensory deficits and significant neuropathic pain [8]. Among the strategies to manage neuropathic pain, the role of anti-inflammatory agents has garnered interest due to the potential inflammatory basis of radiation-induced neuropathy. In this context, the use of icosapent ethyl, a rich source of eicosapentaenoic acid (EPA), may be significant. EPA has demonstrated anti-inflammatory properties, especially targeting neuroinflammation, which has been linked to neuropathic pain [9]. While conventional treatments like tricyclic antidepressants and gabapentinoids remain the mainstay, the incorporation of agents like icosapent ethyl might provide a broader and more effective therapeutic regimen.

Well-established guidelines for treating neuropathic pain comprise a spectrum of pharmacologic agents, among which tricyclic antidepressants, serotonin and norepinephrine reuptake inhibitors, pregabalin, and gabapentin have demonstrated superior tolerability and efficacy [10]. Additionally, omega-3 polyunsaturated fatty acid (PUFA) oral supplements have shown potential benefits in improving peripheral nerve health [11]. These supplements have been found to positively impact nerve conduction and regeneration, and there is limited evidence suggesting they may reduce neuropathic pain [11]. Further research is needed to determine the optimal dosages and long-term effects of omega-3 PUFA supplementation in this context. Given the debilitating nature of RILP, compounded by motor weakness and ambulatory dysfunction, a multidisciplinary treatment approach, which may incorporate a physical therapy program in conjunction with neurostimulation techniques, is crucial [12,13]. Moreover, recognizing the psychological burden chronic pain conditions can impose on patients, the provision of psychotherapy should also be considered.

The use of PBT for the treatment of prostate cancer has been controversial, with some studies suggesting that it may offer benefits over traditional RT, including reduced toxicity and improved quality of life [4]. However, there are concerns regarding the cost-effectiveness of proton therapy and the potential for increased rates of secondary cancers [4]. In addition, the long-term risks of radiation-induced complications, such as neuropathy, are not fully understood and require further investigation.

Our case highlights the potential for radiation-induced neuropathy as a complication of prostate cancer treatment, particularly with the use of PBT. Our patient's medical history and imaging findings demonstrate that the condition can lead to significant morbidity, including weakness and diminished sexual function. To our knowledge, this is the first case of lumbosacral polyradiculitis following PBT for prostate cancer to be reported in the literature.

Given the increasing use of PBT for the treatment of localized prostate cancer, further research is warranted to better understand the risk factors and pathophysiology of radiation-induced neuropathy. In addition, urologists and radiation oncologists should be vigilant in monitoring patients for symptoms of neuropathy following PBT for prostate cancer. Early detection and management of this potentially debilitating complication can significantly improve patient outcomes and quality of life.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper except for Akhil Chhatre, MD: Stryker, consultant. Petal, Scientific advisory board.

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Declaration of competing interest

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