Radiotherapy-induced tumors of the spine, peripheral nerve, and spinal cord: Case report and literature review

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Abstract

Background: The development of a secondary malignancy in the field of radiation is a rare but well-recognized hazard of cancer treatment. The radiotherapy-induced (RT-I) tumors are even more aggressive and potentially lethal than the primary tumor. To goal of this article is to report a case of RT-I neural tumor located in the peripheral nerve and spinal cord and to perform a literature review of the subject.

Case Reports: Thirty-year male with symptoms of hypoesthesia and dysesthesia of the L5 nerve root distribution and previous treatment of a testicular seminoma 20 years previously. The lumbar magnetic resonance imaging showed the growth of a nerve root tumor. Surgery was performed, and a fusiform tumor was resected with clear margins. The anatomopathological and immunohistochemical studies were compatible with a malignant peripheral nerve sheath tumor. A total of 30 cases were included in the review. The mean age of the patients at diagnosis of the induced tumor was 39.36 (±16.74) years. Most were male (63.3%). The main type of primary disease was neural tumors (30%). The most common type of histology was fibrosarcoma (20.0%). No difference was found in age, gender, and time of diagnosis between neural and nonneural tumors. The mean survival after the diagnosis of the secondary tumor was 10.7 months (±13.27), and neural tumors had a longer survival period (P = 0.031).

Conclusion: The current gold standard therapy is complete resection with clear margins, since most tumors do not respond to chemotherapy and RT. The neural type of RT-I tumor presented a longer survival period.

Key Words: Malignant peripheral nerve sheath tumor, radiation-induced tumor, radiotherapy, spine, spine surgery

INTRODUCTION

The development of a secondary malignancy in the field of radiation is a rare but well-recognized hazard of cancer treatment.³⁸ This type of treatment has been associated with an increased rate of solid tumors, specially after Hodgkin’s lymphoma irradiation.¹¹ The first bone tumor secondary to radiotherapy (RT) was described in 1922 by Beck, who reported three cases of the bone tumor after irradiation for tuberculosis.
Even though the risk for developing a new tumor is low, varying from 0.9% to 2%, the long survival time may present a considerable risk for the development of a new tumor. Tsang et al. reported a relative risk of 1.8/10,000 persons per year. The RT-induced (RT-I) tumors are even more aggressive and potentially lethal than the primary tumor.

Usually, the site of the RT-I tumor is the periphery of the radiation field. In general, the most common type of radiation-induced tumor of the spine is bone and soft tissue sarcoma, neural tumors being more unusual. The capacity to induce secondary neural tumors requires the higher doses of radiation, and the mean latency period can reach 10 years.

RT-I tumors have become increasingly important because of the longer life of the general population, even the oncologic patients. The goal of this study is to report a case of neural tumor secondary to RT and to perform a literature review on the cases of RT-I tumors of the spine.

**CASE REPORT**

A 30-year-old male presented with symptoms of hypoesthesia and dysesthesia of the L5 nerve root distribution, with right positive Lasègue, and normal strength and reflexes for 60 days. The patient presented no comorbidities, except the previous treatment of a testicular seminoma with orchiectomy and adjuvant RT 20 years ago. The radiation dose utilized for the treatment of the seminoma was 30.6 Gy, irradiating the cervical and para-aortic regions. There was no personal or family history of neurofibromatosis. He had undergone coronal, sagittal, and axial T2-weighted contrast-enhanced magnetic resonance imaging (MRI) of the lumbar spine that revealed a contrast enhancement of two nodular formations placed in the L4 nerve root, the first located proximally, measuring 1.1 cm × 0.6 cm, and the second distally in the right lateral recess of the spinal canal, measuring 2.1 cm × 0.9 cm. Investigation with a neurophysiologic study of lower limbs, genetic analysis, and brain, cervical, and thoracic MRI was indicated.

The results of the electroneuromyography of lower limbs revealed subacute and chronic right L5 neuropathy without muscle denervation. The genetic analysis was normal. The brain and cervical spine MRI were normal.

A surgical indication for diagnosis and treatment as well its complications were discussed with the patient and his family. The patient was afraid of motor deficit complications and decided to control the pain with physiotherapy and oral analgesic medication. The patient was closely observed. The pain was well-controlled with physiotherapy and oral analgesia when necessary during 6 months. After this period, the patient complained of a progressive increase of sciatica, the paresthesia became worse, and the motor strength was quickly and severely reduced with Grade 2 dorsiflexion of the right foot strength. The lumbar MRI showed that a tumor of the nerve root had grown.

Surgery was indicated and accepted by the patient and his family. The surgical planning was total tumor removal with free margins. A right hemilaminectomy from L3 to S1 was performed. After the incision of the dura mater, a fusiform tumor was visualized adjacent to the L5 foramen and adjacent of the cauda equina nerve roots. The L4 nerve root was individualized and sectioned proximal to the upper margin of the tumor. The distal tumor was dissected, and the nerve root distally to the tumor was individualized and sectioned. The entire segment of L4 nerve root was resected with clear margins.

The dura mater was sutured with 4.0 mononylon. The paravertebral muscle was tightly sutured to avoid cerebrospinal fluid (CSF) leak. The subcutaneous tissue and skin layer were closed in the standard fashion.

The patient was discharged from hospital 3 days after surgery with better resolution of pain, hypoesthesia in the L5 dermatomes, and motor strength Grade 3 of the L5 nerve root. The anatomopathological and immunohistochemical studies showed a hypercellular malignant spindle cell tumor with a high mitotic index and moderate pleomorphism in a nerve root, compatible with a malignant peripheral nerve sheath tumor (MPNST).

Thirty days later the patient reported somnolence, anisocoria, diplopia, severe Grade 2 paraparesis, neurogenic bowel with flaccid anal sphincter tone, and neurogenic bladder.
T1-weighted contrast-enhanced MRI of brain and spine demonstrated a hypertensive hydrocephalus, leptomeningeal enhancement, and contrast-enhanced masses throughout the cervicothoracic spinal cord surfaces [Figure 2b]. The patient underwent urgent cervical decompression via C7-T2 laminectomy with partial resection of the fibrous tumor and a ventricular catheter to monitor intracranial pressure and CSF drainage. Biopsy staining with hematoxylin and eosin revealed features characteristic of the malignant peripheral nerve sheath.

The patient died from acute respiratory failure 48 h after the second surgery. The patient’s total time of survival from the time of MPNST diagnosis was 9 months.

**DISCUSSION**

Cahan and Woodard [7] proposed that the following criteria should be fulfilled for a sarcoma to be considered as radiation-induced: (1) The sarcoma should begin in the area subjected to irradiation, (2) a latent period (in years) must exist between the time of irradiation and the development of the sarcoma, and (3) the sarcoma must be diagnosed histologically. The case reported fulfills all these criteria.

The case reported had undergone adjuvant RT for testicular seminoma 20 years before presenting with an RT-I intradural MPNST that developed diffuse leptomeningeal, hydrocephalus, and cervicothoracic spinal cord metastases. A literature review of RT-I spine tumor cases was performed in an online database: pubmed.gov (http://www.ncbi.nlm.nih.gov/pubmed/)
Figure 5: Literature review of radiation-induced tumors of the spine using an online database of pubmed.gov

[Figure 5] A total of 30 cases were included, 29 cases reported in the literature from 22 articles and the case presented in this paper [Table 1]. The mean age of RT-I spine tumor cases was 39.36 (±16.74) years at the diagnosis of the induced tumor, and most of them were male (63.3% - 19/29).

According to Toland et al.[39] in 643 cases of Hodgkin’s lymphoma treated with RT, 18 presented secondary malignancies. RT in the treatment of Hodgkin’s lymphoma dramatically increased the patients’ survival but also increased the incidence of RT-I tumors cases. The incidence of RT-I tumors was also observed after RT for testicular cancer with a 2.6-fold increased risk.[42] To avoid this complication, the therapy guideline for testicular cancer was modified, for example, by the use of carboplatin as an alternative instead of RT.[2,30,31,43]

The pathology of the primary tumor of the 30 spine tumors cases induced by RT was mainly neural tumors (30%), followed by Hodgkin’s lymphoma (16.6%), ankylosing spondylitis (16.6%), seminoma (13.3%), and astrocytoma (10.0%) [Table 1]. The most common site of the primary tumor was the sacral region (21.4%) followed by testicle (14.3%), mediastinum (10.3%), and cervix (10.3%) [Table 1].

Prompt recognition and treatment of radio-induced tumors located in the spine are crucial because they tend to grow rapidly and have a low response to conventional radiation and chemotherapy.[38] However, it is not always easy to recognize them. The clinical presentation frequently mimics benign disc disease, which may lead to a wrong diagnostic and surgical approach only for decompression,[38] or even mimic the recurrence of the original tumor.[8,16] The radiological and pathological findings are indistinguishable from a spontaneous solitary osteochondroma,[17] and due to its latent period of appearance after the irradiation, the differential diagnosis with late onset metastasis is difficult.[38]

In the reported case, the MRI diagnosis was two small nodular lesions in peripheral nerve compatible with a benign tumor of nerve sheath. This radiological presentation was concordant with the symptoms, and the neurophysiologic study of lower limbs. The genetic analysis was performed to evaluate the presence of neurofibromatosis with a normal result. To identify others lesions in the neuroaxis, brain, cervical, and thoracic MRI were indicated and did not show any tumor except those in the lumbar region. At that time, the patient decides to treat the pain and be closely observed because he was afraid of the chance of residual motor deficit from surgery.

The cases of RT-I tumors reported in the literature were diagnosed on average 16.6 (± 9.73) years after the RT (minimum 3 – maximum 40) [Table 1]. The thoracic spine (26.7%) was the most common location involved followed by sacral (23.3%), cervical (20.0%), lumbar (10.0%), and combined spinal segments in the rest of the cases (20.0%) [Table 1].

The most common type of RT-I tumor in the spine was fibrosarcoma (20.0%) followed mainly by MPNST (16.6%), osteosarcoma (13.3%), and osteochondroma (10.0%) [Table 1]. MPNST are extremely rare tumors with an incidence of 0.001% in the general population.[1,44] In the present review, four MPNST (13.3%) located in the spine were reported as secondary to RT, and these tumors are considered aggressive with a poor long-term prognosis.[38]

Surgery is the main therapy in these cases (56.7%), especially because no clear survival benefit has been demonstrated with RT or chemotherapy [Table 1].[44] In the case we reported, there was a two-nodule formation in the right L5 nerve root. Despite aggressive surgical resection, the patient went on to have diffuse leptomeningeal spread and seeding of the cervical spinal cord dysfunction and hypertensive hydrocephaly and died despite prompt treatment.

In patients with a history of previous RT that had a clinical presentation of the spine and/or spinal cord dysfunction and where a lesion is detected, a biopsy should be performed to rule out a second primary neoplasm.[38] In those cases, the current gold standard of the treatment is complete resection with clear margins.[3] Aggressive surgical management significantly improves survival when adequate margins are obtained.[22] However, the possibility of obtaining wide margins for spinal tumors is about 20%, given their proximity to or invasion of the spinal cord, major vessels, and peripheral nerves.[14,20,25]
Table 1: Summary of the systematic review of the 28 cases of radio-induced of the spine reported in the literature

| Author (year)                        | Age (years) | Primary tumor location - histology | Total intensity of radiotherapy for primary tumor | Location of radiation-induced tumor | Histological type                        | Diagnosis after primary tumor (years) | Treatment option                        | Survival after diagnosis of radio-induced tumor (months) |
|-------------------------------------|-------------|-----------------------------------|--------------------------------------------------|-----------------------------------|------------------------------------------|----------------------------------------|----------------------------------------|----------------------------------------------------------|
| Falavigna (2014)                    | 30 - male   | Testicle - seminoma               | 30.6 Gy (T10–T12)                                 | Thoracic and lumbar                | Malignant peripheral nerve sheath         | 20                                     | Surgical                               | 9 DD                                                     |
| Kawanabe et al. (2012)              | 54 - male   | Testicle - seminoma               | 30.6 Gy (periaortic + sacrum)                      | Sacral                            | Anaplastic astrocytoma                   | 37                                     | Surgical + chemotherapy                 | 9 DD                                                     |
| West et al. (1997)                  | 40 - male   | Testicle - seminoma               | 5400 r (SI + TL + TC)                              | Lumbar                            | Fibrosarcoma                             | 20                                     | Surgical                               | 11 DD                                                    |
| Edgar and Robinson (1973)[15] Case 1| 26 - male   | Sacral - ankylosing spondylitis   | 1360 r (SI)                                       | Sacral                            | Fibrosarcoma                            | 17                                     | Surgical                               | 6 DD                                                     |
| Edgar and Robinson (1973)[15] Case 2| 19 - male   | Sacral - ankylosing spondylitis   | 2000 r (CT)                                       | Sacral                            | Fibrosarcoma/leiomyosarcoma              | 15                                     | NR                                     | 6 DD                                                     |
| Edgar and Robinson (1973)[15] Case 3| 41 - male   | Sacral - ankylosing spondylitis   | 11,600 r (SI + L)                                 | Lumbar                            | Fibrosarcoma                            | 9                                      | Surgical                               | 6 DD                                                     |
| Edgar and Robinson (1973)[15] Case 4| 18 - male   | Lumbar - ankylosing spondylitis   | 15,910 r (SI + TL + TC)                            | Sacral                            | Fibrosarcoma                            | 17                                     | Palliative irradiation                  | 3 DD                                                     |
| Noh and Huh (2007)[36] Case 1       | 59 - female | Uterine - cervical adenocarcinoma | 50 Gy (pelvic)                                    | Sacral                            | Osteosarcoma                            | 16                                     | Chemotherapy + palliative radiotherapy | 2 LLF                                                    |
| Noh and Huh (2007)[36] Case 2       | 66 - female | Uterine - squamous cell carcinoma | 54 Gy (pelvic)                                    | Sacral                            | Sarcoma                                 | 7                                      | Palliative radiotherapy                  | ? LLF                                                    |
| Amin et al. (2004)[31]              | 38 - male   | Testicular - seminoma             | 30 Gy (para-aortic)                               | Thoracic and lumbar                | Malignant peripheral nerve sheath tumor  | 10                                     | Palliative radiotherapy                  | NR the LLF                                               |
| Amirjamshidi and Abbasiouen (2000)[4] | 17 - female | Cerebellar - ependymoma          | 2000 r (spine)                                    | Cervical                          | Meningotheliomatous meningioma           | 15                                     | Surgical + chemotherapy + radiotherapy | 58 LLF                                                   |
| Marzbani et al. (2013)[29]          | 65 - male   | Thoracic - astrocytoma           | 50.4+30 Gy (T1–T7)                                | Thoracic and lumbar                | Rhabdomyosarcoma                        | 40                                     | Surgical + radiotherapy                  | 8 DD                                                     |
| Ng et al. (2007)[34]                | 26 - male   | Mediastinal - Hodgkin lymphoma    | 3060 cGy (mediastinal)                            | Thoracic                          | Astrocytoma                             | 3                                      | Surgical + radiotherapy + chemotherapy | Several weeks DD 13 DD                                   |
| Mut et al. (2004)[32]               | 36 - male   | Thoracic - aneurysmal bone cyst   | 65 Gy (thoracic)                                  | Cervical                          | Rhabdomyosarcoma                        | 7                                      | Surgical + chemotherapy                 | NR the LLF                                               |
| Gorospe et al. (2002)[17]           | 18 - male   | Cerebellar - medulloblastoma      | 7950 rad (cranial + spine)                        | Thoracic                          | Osteochondroma                          | 11                                     | Surgical                               | <1 week LLF                                              |
| Leis and Fratkin (1997)[28]         | 34 - male   | Hodgkin lymphoma                  | 4000 (cranial + CT)                               | Thoracic                          | Chondrosarcoma                          | 24                                     | Surgical                               | NR the LLF                                               |

Contd...
The overall prognosis for patients with secondary RT-I tumors in the spine is dismal because there are no proven benefits of chemotherapy, RT, intraoperative electron irradiation, and brachytherapy, with a 5-year survival rate of around 20\% \([5, 37, 41]\). The mean survival after the diagnosis of the secondary tumor was 10.7 months \((\pm 13.27)\). The majority of the patients (63.3\%) died from the disease, and 26.6\% were alive at the last follow-up \([Table 1]\). The analysis comparing neural and nonneural RT-I tumors showed a longer survival period of 9.0 \((\pm 17.0)\) months in neural tumor cases, compared to 6.0 \((\pm 8.3)\) months in patients with nonneural tumors \((P = 0.039)\) \([Table 2]\). The age, sex, and time of diagnosis were similar in the neural and nonneural groups.

**Table 1: Contd...**

| Author (year) | Age (years) - gender | Primary tumor location - histology | Total intensity of radiotherapy for primary tumor | Location of radiation-induced tumor | Histological type | Diagnosis after primary tumor (years) | Treatment option | Survival after diagnosis of radio-induced tumor (months) |
|--------------|----------------------|-----------------------------------|-----------------------------------------------|-----------------------------------|------------------|-------------------------------------|-----------------|-----------------------------------------------|
| Isler et al. (1996)\([22]\) | 46 - male | Sacral - chordoma | 4960 rad \((14\text{-sacrum})\) | Lumbar | Neurofibroma/schwanoma | 9 | Surgical | 24 DD |
| Kam et al. (2013)\([23]\) | 68 - female | Breast - carcinoma | 15 Gy \((\text{thoracic})\) | Thoracic | Fibrosarcoma | 30 | Surgical | Not reported |
| Cree et al. (1994)\([11]\) | 29 - female | Abdominal - neuroblastoma | 2500 rad \((10 \text{ cm} \times 15 \text{ cm})\) | Lumbar | Osteochondroma | 28 | Surgical | 3 LLF |
| Nadeem et al. (1991)\([33]\) | 36 - male | Cervical - astrocytoma | 4500 cGy \((\text{cervical})\) | Cervical | Histioctomy + ependymoma | 12 | Surgical + radiotherapy + chemotherapy | 3 DD |
| Sundaresan et al. (1986)\([38]\) | 59 - female | Mediastinal - Hodgkin lymphoma | 4400 rad \((\text{thoracic})\) | Thoracic | Telangiectatic osteogenic sarcoma | 31 | Surgical + chemotherapy | 3 DD |
| Dowdle et al. (1977)\([13]\) | 14 - female | Cervical - astrocytoma | 4500 rad \((\text{cervical})\) | Thoracic | Osteosarcoma | 11 | Surgical | 1 DD |
| Scheiden and Oberthaler (1983)\([36]\) | 41 - male | Sacrum - cystic tumor | 27000 rad \((\text{cervical})\) | Sacral | Osteosarcoma | 20 | Surgical | 12 DD |
| Herman et al. (1991)\([18]\) | 16 - female | Kidney - Wilms tumor | 3000 rad \((\text{abdominal})\) | Thoracic | Osteochondroma | 15 | Surgical | NR |
| Lang et al. (1981)\([26]\) | 60 - female | Vocal cord - malignant epithelioma | 7500 rad \((\text{cervical})\) | Cervical | Osteosarcoma | 11 | Surgical | 3 DD |
| Adamson et al. (2004)\([1]\) Case 1 | 37 - male | Mediastinal - Hodgkin lymphoma | 7200 cGy \((\text{mediastinal + para-aortic})\) | Cervical | Malignant peripheral nerve sheath tumor | 6 | Surgical + radiotherapy | Few months DD |
| Adamson et al. (2004)\([1]\) Case 2 | 31 - female | Cervical lymph node - Hodgkin lymphoma | 7700 cGy \((\text{mantle + para-aortic})\) | Cervical | Malignant peripheral nerve sheath tumor | 16 | Surgical | 12 DD |
| Hu et al. (2010)\([21]\) | 66 - male | Thyroid | 7000 cGy \((\text{cervical} 12 \text{ cm} \times 15 \text{ cm})\) | Cervical | Sarcoma | 30 | Surgical | 29 LLF |
| Comey et al. (1998)\([14]\) | 44 - male | Cerebellopontine - triton tumor | 34 Gy \((\text{cerebellopontine})\) | Cervical | Triton tumor | 4 | Surgical | 6.5 DD |

LLF: Live at last follow-up, DD: Died from disease, SI: Sacroiliac, TL: Thoracolumbar, TC: Thoracocervical, NR: Not reported

**Table 2: The analysis comparing neural and nonneural tumors**

| | Neural tumor (%) | P |
|---|---|---|
| **Age (mean±SD)** | 36.27 (±10.14) | 41.15 (±19.63) | 0.377* |
| **Gender** | 9 (47.4) | 10 (52.6) | 0.140* |
| Male (63.3%) | 2 (18.2) | 9 (81.8) | |
| Female (36.7%) | | | |
| **Time for diagnosis (mean±SD)** | 12.72 (±9.58) | 18.89 (±9.32) | 0.095* |
| **Survival in months (median±IQR)** | 9.0 (±17.0) | 6.0 (±8.3) | 0.039* |

*T-test, *Chi-square test, *Mann–Whitney U-test. SD: Standard deviation, IQR: Interquartile range
CONCLUSION

RT-I tumors of the spine, peripheral nerve, and spinal cord are not common. Twenty-nine cases have been reported in the literature. Better awareness of this entity and its potential for metastasis to the central nervous system may enable physicians to perform early intervention. The current gold standard therapy is complete resection with clear margins, since most tumors do not respond to chemotherapy and RT. The neutral type of RT-I tumor presented a longer survival.

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Conflicts of interest
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