Case Report

Radiation Induced Osteosarcoma of the Larynx: A Rare Case Report

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DOI: 10.21276/APALM.3283

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Submitted: 03-Nov-2023
Final Revision: 15-Dec-2023
Acceptance: 21-Dec-2023
Publication: 05-Jan-2024

Abstract

Secondary malignancies caused by radiation, especially radiation-induced sarcomas (RIS), are perhaps the most severe late side effects of radiotherapy. The incidence of sarcomas after irradiation is estimated to be as high as 0.3% in those who have survived neck and head cancer for a long time. Nevertheless, it is also accompanied by significant morbidity and mortality. RIS of the head and neck is not prevalent. As there are only a limited number of case reports, we report a case of radiation induced osteosarcoma from our institution.

Case report: A 67 year old male patient, previously treated for squamous cell carcinoma larynx with radiotherapy 60 gy, presented to our institution with complaints of hoarseness of voice. CT Neck showed an ill-defined heterogeneously enhancing mass lesion in the larynx with extra laryngeal extension and causing erosion of the thyroid cartilage. He was subsequently taken for total laryngectomy. Histopathological examination showed a high-grade malignant neoplasm. Further IHC revealed tumor cells diffusely positive for SATB2 and negative for PanCK, p63 and p40. He was diagnosed with high grade osteosarcoma and was taken up for adjuvant chemotherapy.

Conclusion: As there are only limited case reports, more number of cases should be reported for further discussion about the adjunctive treatment options and prognosis.

Keywords:

Radiation induced sarcomas, Osteosarcoma, IHC, Adjuvant chemotherapy

Introduction

Radiation therapy (RT) is a core pillar of oncologic treatment, and an estimated 50% of all patients with cancer receive RT as a treatment modality.[1,2]Although RT is an effective means to treat the primary malignancy and prevent disease recurrence, it is a “double-edged sword” that carries substantial morbidity due to both acute and chronic adverse effects.[3] RT-induced malignancies (RTIMs) are late complications that occur in patients who receive RT, with variable latency, At present after surviving a primary malignancy, 17%–19% of patients develop a second malignancy. The reported second malignancies after RT include sarcomas, carcinomas, leukaemia, and mesotheliomas. Radiation-induced second malignancies, particularly radiation-induced sarcomas (RIS), are arguably the most devastating sequelae associated with radiotherapy. Squamous cell carcinoma comprises the most common histologic sub-type of radiation-induced malignancy. RIS is the second most common, accounting for approximately 12% of radiation-induced malignancies and the lifetime risk has been estimated to be 0.03%-0.3% in patients

who have been previously radiated.

The most common histologic subtypes of RIS parallel their de novo counterparts and include osteosarcoma, chondrosarcoma, malignant fibrous histiocytoma and fibrosarcoma. The incidence of laryngeal sarcoma is exceedingly low with osteosarcomas of the larynx being rarer still, comprising less than 1% of all associated malignancies. To date, only 32 cases have been reported since this pathologic entity was first described in 1942. Out of the 32 cases, only 3 cases (9%) of laryngeal osteosarcomas have been reported to be radiation induced.[4] The first case of post irradiation laryngeal osteosarcoma was described by Sheen et al in 1997.[5] We present a case of post radiation osteosarcoma of the larynx including radiological and pathological findings, treatment and outcome.

Case Report

Our case was that of a 67-year-old male patient, who was a known case of squamous cell carcinoma, right vocal cord (T1). He was treated with radiotherapy 60 Gy in 20 fractions, completed in 2010 from another institution. Now the patient presented with hoarseness of voice since 5 months. Computed Tomography(CT) Neck and Thorax showed a ill-defined heterogeneously enhancing lesion with calcification noted in the left vocal cord with erosion of the left lamina of thyroid cartilage with extra laryngeal extension.(Fig 1) The lesion measured 3x2.6x2.7 cm. Patient underwent total laryngectomy with posterolateral neck dissection. We received laryngectomy specimen measuring 8.5x5x4,5cm . The specimen was opened along posterior midline to reveal a glistening lesion measuring 2.5x2.5x 2 cm in the left glottis and subglottis with overlying edematous but intact mucosa. Microscopy showed a high grade tumor composed of sheets of cells with extensive areas of sclerosis, osteoid formation and focal areas of ossification. The tumor cells were plump to spindled with pleomorphic hyperchromatic nucleus and moderate cytoplasm(Fig 2,3). The tumor was seen infiltrating into the thyroid cartilage and strap muscle. Further IHC evaluation revealed tumor cells diffusely positive for SATB2 and negative for PanCK, p63 , p40, Desmin and S100(Fig4). The case was reported as High grade Osteosarcoma . No lymphovascular/ perineural invasion was identified in our case. The case was discussed in head and neck multidisciplinary team (MDT) and was planned for adjuvant chemoradiation. The patient is on follow-up and has completed adjuvant chemoradiation, repeat CT scan showed no metastasis. He is currently undergoing esophageal speech therapy and has no other fresh complaints.

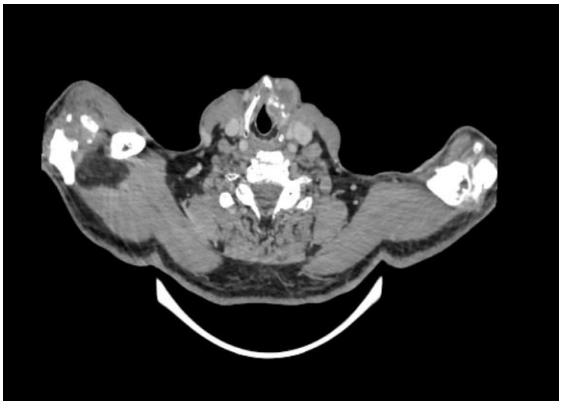

Figure 1: CT Scan showed a ill defined lesion involving the left vocal cord with erosion of the left lamina of thyroid cartilage with extralaryngeal extension.

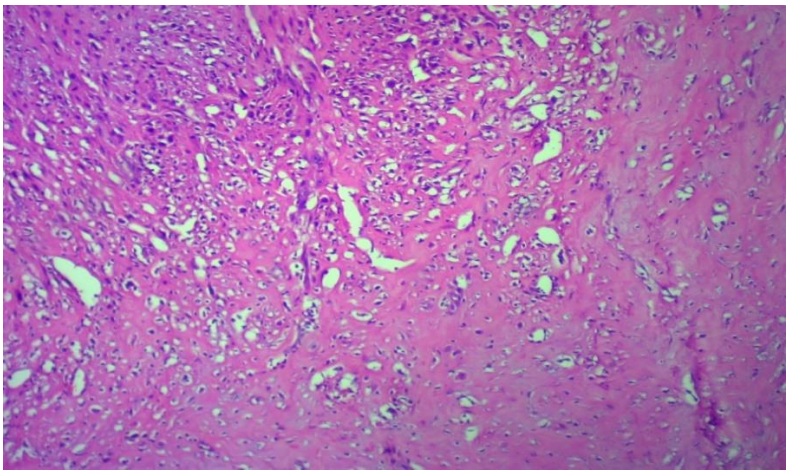

Figure 2: Section shows neoplastic cells and osteoid formation. (H&E, 10X)

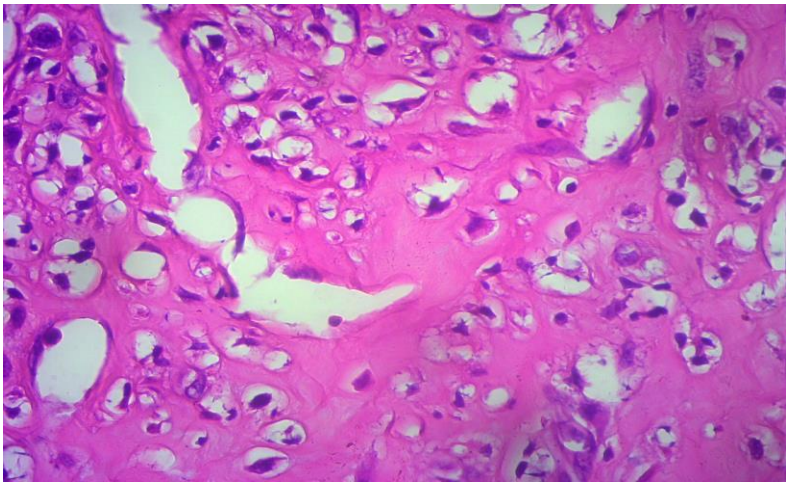

Figure 3: Neoplastic cells with pleomorphic hyperchromatic nucleus and osteoid formation. (H&E,40X)

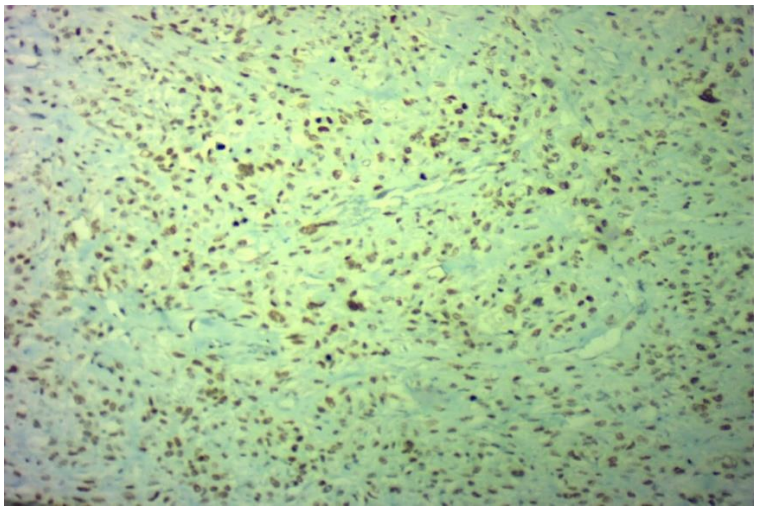

Figure 4: The tumour cells show diffuse positivity for SATB2. (IHC,40X)

Discussion

Radiation therapy has been an effective treatment of many benign and malignant lesions since its inception in the late 19th century. However, it was not long before the risk of radiation-induced tumorigenesis was first recognized. Radiation-induced malignancies were initially described by Freiben et al in 1908 [6] and subsequently, in 1948, Cahan et al[7] outlined the first diagnostic criteria for radiation-induced sarcoma (RIS) and then revised by Murray et al.[8] These criteria include (1) the tumor arises in a field that has been previously irradiated (2) the subsequent tumor differs histologically from the first tumor, (3) no history of the new tumor at the time of RT, and (4) the new tumor is developed after a latency period following RT.

Second malignancies in survivors of cancer constitute 19% of all cancer diagnoses in the United States, and when data for cancer survivors are compared with those of the general population, there is a 14% higher rate of cancer among survivors.[9] The reported risk factors for second cancers include prior treatment (chemotherapy and Radiotherapy), environmental and lifestyle exposures, and genetic susceptibility.

The common histological subtypes of Radiation-induced tumors are squamous cell carcinoma (SCC) followed by sarcoma, even though many types of cancers have been described after radiotherapy (RT). Laskin et al[10] reported that 12% of radiation-induced tumors were sarcomas.

RI sarcomas of the head and neck (RISHN) are very rare entities and characterized by poor long-term outcomes. Their incidence is quite low and variable: among the largest retrospective studies available in the literature, the reported annual incidence was 0.06–0.17%,[11] compared to a 1.6% incidence when all body RIS were considered. RIS includes osseous and soft tissue sarcomas, and the vast majority are high-grade. The most common histologic subtypes of RIS include osteosarcoma, chondrosarcoma, malignant fibrous histiocytoma and fibrosarcoma.

Approximately 0.32% of malignant tumors in the larynx are sarcomas. Fibrosarcomas and chondrosarcomas are the most common variants and osteosarcoma is the rarest. Radiation-induced osteosarcoma of the larynx is a rare,but aggressive tumour first described by Sheen et al in 1997. The median time of latency after RT is reported to be 10– 12 years, while the arbitrary cut-off used to distinguish RIS(Radiation induced sarcoma) from sporadic sarcomas is 3–4 years after RT. The development of radiation-induced sarcomas may be influenced by factors such as dose, age at initial exposure, to chemotherapeutic agents, and genetic tendency. The precise pathogenetic mechanisms underlying susceptibility to and development of radiation-induced tumors are poorly understood. The prevailing paradigm focuses on radiation-induced DNA damage leading to mutations in susceptible cells. In this regard, p53 point mutations and genetic aberrations in the Rb gene have been implicated.[12,13]

Sarcomas of the larynx can be divided into two categories: primary tumors, which arise de novo, and secondary tumors, such as radiation-induced tumors or those associated with Paget disease. Osteosarcoma is a malignant mesenchymal tumor in which the neoplastic cells produce osteoid tissue. Although osteosarcomas are the most common bone tumor, they are extremely rare in the larynx.[14] Macroscopically, the neoplasm is mainly polypoid or exophytic in appearance but may also mimic other sarcomas. Microscopically, the tumor is composed of frankly malignant, spindle-shaped mesenchymal cells, associated with osteoid and immature neoplastic bone formation, uniform or pleomorphic,hyperchromatic, bizarre nuclei with frequent mitotic figures. Giant cells resembling osteoclasts are often present. Immunohistochemical staining has shown that the neoplasm is positive for SATB2, vimentin ,and negative for Desmin, S-100 protein, cytokeratin (AE1/AE3, MNF-116, CK5/6, CK7, CK8, CK19, CK20), and epithelial membrane antigen.

The most common presenting complaints in laryngeal osteosarcoma are hoarseness and dyspnea, usually arising within the 6-month period before the patient's presentation. Paget disease, radiation exposure, exposure to thorium oxide,fibrous dysplasia, retinoblastoma, and p53 mutations are risk factors for osteosarcoma. Smoking and alcohol have not been confirmed as risk factors.

Ulusan et al[15] in a review of published cases, found only 23 laryngeal osteosarcomas reported by 2012. Among those cases, 2 were metastatic, and 2 occurred secondary to radiation exposure .In the first radiotherapy-induced case, radiotherapy had been performed for a nasopharyngeal carcinoma 32 years previously. The patient in the second radiation-induced case had undergone a partial laryngectomy for laryngeal squamous cell carcinoma followed by chemoradiation 4 to 5 years before the osteosarcoma was detected. In our case the latency period was 12 years.

In two reported cases in the literature, the patients were treated with radiotherapy alone; both had local failure and the patients died within 24 months. The best treatment choice for laryngeal osteosarcoma has not been determined because of the disease's rarity. Surgery, radiotherapy, and chemotherapy have all been utilized.

Conclusion

Radiation- induced osteosarcoma of the larynx is extremely rare. As there are only a limited number of case reports, there is no consensus regarding the management of laryngeal osteosarcoma. Surgical resections with negative margin is the current treatment as it offers the best chance for long term survival. Adjuvant chemotherapy and re-irradiation may have a role in carefully selected cases. Future studies analyzing the genetics of RIS are also warranted to identify mechanisms responsible for sarcomagenesis and might be very helpful in finding possible new and effective drugs.

Acknowledgements: None
Funding: None
Competing Interests: None

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