CASE REPORT

Radiation-induced leiomyosarcoma: does antimetabolite chemotherapy contribute? A report of three cases

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Abstract

Purpose: Radiation therapy in low and high doses is known to be associated with the occurrence of late secondary sarcomas. The addition of chemotherapy has not been clearly demonstrated as a contributing factor. We describe three patients with radiation-associated leiomyosarcoma who had also received antimetabolite chemotherapy.

Methods: Three cases of leiomyosarcoma occurring 9–27 years after radiation and antimetabolite chemotherapy are presented, along with histopathological details. A Medline search was used to assess prior reports of leiomyosarcoma after radiation.

Results: These three cases appear to be the first reported in which leiomyosarcoma followed therapy with radiation and antimetabolites.

Discussion: With the increasing use of antimetabolite therapy combined with radiation, there is the potential for more occurrences of leiomyosarcoma or other post-treatment sarcomas.

Key words: leiomyosarcoma, radiation, chemotherapy, antimetabolite, secondary malignancy

Introduction

There is a clear association between radiotherapy and an increased risk of development of secondary solid tumors, including sarcomas.^{1–11} Patients treated with radiotherapy (RT) for Hodgkin's disease have a risk as high as 20% at 20 years, and much of this excess risk is attributable to radiotherapy with or without chemotherapy.^{12,13} Therapeutic radiation for other malignant and benign diseases has also been associated with secondary malignancies, including secondary sarcomas.^{14,17} Numerous histological subtypes of secondary sarcoma have been reported, but the most common have been osteosarcoma, fibrosarcoma, malignant fibrous histiocytoma (MFH), and angiosarcoma. Leiomyosarcoma (LMS) has been reported to occur after radiotherapy, but mostly in single case reports, and several very small series. These LMS have occurred in diverse sites, after 6–35 years, and after treatment for a variety of malignancies.^{18–42}

In this report, we describe a series of three patients who developed leiomyosarcoma in the field of

therapeutic radiation after 9–27 years. All had also been treated with antimetabolite chemotherapy.

Patients and methods

We performed a Medline search encompassing the dates 1966–2001. Search terms were used to link radiation therapy, chemotherapy, antimetabolites, and Hodgkin's disease to secondary malignancies, solid tumors, sarcoma, and leiomyosarcoma. Reports of radiation-associated leiomyosarcoma were reviewed for elapsed time between RT and secondary leiomyosarcoma, as well as association of chemotherapy with RT. The cases are summarized in Table 1.

Case reports and results

Case 1

A 71-year-old man was treated in 1984 for rectal cancer with a low anterior resection and post-operative 5-fluorouracil, together with radiotherapy

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Table 1. Summary of cases

Pt.	Initial tumor	Initial treatment	Prior RT		Second primary		Comments
			Date	Dose (Gy)	Date	Site	
1	Rectum	RT 5-Fluorouracil	1984	50.4	1998 (14 years)	Buttock	LTFU
2	Face	RT Cyclophosphamide azathioprine	1971 1984	21 45	1998 (14/27 years)	Maxillary sinus	Doxorubicin + Ifosfamide → Surgery → NED
3	Larynx	RT 5-Fluorouracil, hydroxyurea	1989	60	1998 (9 years)	Trachea	Doxorubicin + dacarbazine → Died
ALL RT plus antimetabolite			9–27-year interval				

LTFU, lost to follow-up; NED, no evidence of disease; RT, radiotherapy; Gy gray.

Fig. 1. (a) Low power H&E stain reveals a diffusely elongated spindle cell neoplasm from a 1.5-cm tumor. (b) Representative high power view of immunostain for smooth muscle antigen (SMA). Additional stains for desmin, muscle specific antigen, keratin, HMB45, and S100 were negative.

(5040 cGy radiation). A solitary liver metastasis was resected in 1990. He developed a spontaneous pneumothorax in September 1998, which recurred after chest tube evacuation. A CXR and subsequent chest CT scan showed bilateral pulmonary nodules. A thoracoscopic biopsy revealed a high-grade leiomyosarcoma (Fig. 1). The patient had a 1-year history of posterior thigh and buttock pain; clinical examination demonstrated a large deep left buttock mass. CT scan demonstrated the primary tumor as an $8 \times 5 \times 4$ -cm mass deep to the left gluteal muscles, and a 6-cm ring enhancing collection posterior to the rectum.

Case 2

A 60-year-old man had a 30-year history of relapsing 'midline destructive disease' and an acoustic neuroma diagnosed in 1995. Aggressive disease over the years resulted in disease-related and surgical loss of nasal and facial bone and cartilage. Extensive past treatment included antibiotics, cyclophosphamide, azathioprine, and multiple surgical procedures. He received radiation to the midline face in 1971 (2100 cGy Cobalt radiation) and again in 1984 (4500 cGy; the exact timing of the azathioprine and cyclophosphamide in relationship to the two courses

Fig. 2. (a) High power H&E stain reveals a pleomorphic high-grade spindle cell neoplasm. (b) Representative high power view of immunostain for SMA. SMA, as well as muscle specific antigen, is clearly positive in pleomorphic malignant tumor cells. Desmin and Leukocyte common antigen were negative, and S100 and keratin showed occasional positivity. (LMS may occasionally show keratin positivity.)

of radiation is not known). In June 1998 he noted a small mass beneath the left eye. A work-up included a CT scan of the sinuses, which showed a large mass involving the left face in the area of the left maxillary sinus with extensive destruction of the adjacent bony structures and extension into the ethmoid and sphenoid sinuses. A biopsy in October 1998 revealed a high-grade leiomyosarcoma (Fig. 2). The patient had a dramatic response to three cycles of pre-operative doxorubicin and ifosfamide. Surgical excision of the tumor revealed only microscopic deposits of residual LMS. Two additional cycles of chemotherapy were given, and the patient remained free of disease 1 year later.

Case 3

A 76-year-old woman was treated for a T2N0M0 squamous cell carcinoma of the epiglottis in 1989 with laser excision and post-operative infusional 5-FU (800 mg/m² per day $\times$ 5 days every other week for six cycles), oral hydroxyurea (1000 twice daily for 5.5 days, every other week for six cycles) and radiation (6000 cGy). In October 1998, the patient presented with dysphagia and stridor; direct laryngoscopy and CT scanning revealed a large, partially obstructing tracheal mass (Fig. 3). A tracheal stent was placed, and a biopsy revealed a high-grade leiomyosarcoma (Fig. 4). The mass was unresectable, and she underwent palliative chemotherapy with doxorubicin and dacarbazine in November

1998. She tolerated the chemotherapy well but died within a month of disease progression.

Discussion

We report three cases of radiation associated LMS occurring 9–14 years following RT (or 9–27, as one patient received two separate courses of RT) in three patients who presented to our clinic in the same month. All had received prior antimetabolite therapy: in one case, 5-fluorouracil; in another azathioprine; and in the third, 5-fluorouracil and hydroxyurea. One of these patients also received the alkylating agent cyclophosphamide.

Clear associations have been made between therapeutic RT for cancer and the development of late second malignancies.^{1–7} These associations have also been made for low-dose RT as used in the past for benign conditions such as tonsillar enlargement, menorrhagia, peptic ulcer disease or acne.^{8–10} An excess of hematological malignancies and solid tumors occur above that expected for either age-matched controls or disease-matched controls not receiving radiation. Even though soft tissue sarcomas represent only a small percentage of these solid tumors, the excess relative risk at 20 years has been reported to be six- to several hundred-fold greater than expected.^{2,6,11} Whereas there appears to be a plateau in the incidence of hematological malignancies at 10 years, the peak solid tumor incidence has not been identified, and series with 15–20 year

Fig. 3. CT of neck with intravenous contrast shows tracheal mass growing through tracheal ring stent.

Fig. 4. (a) High power H&E reveals a spindle cell neoplasm with marked nuclear atypia and abnormal mitotic figures. (b) High power SMA stain supports the diagnosis of leiomyosarcoma. Additional stains included vimentin (positive) and keratin (negative).

follow-up report a total incidence as high as over 20%.^{1,3,5,11,12}

Chemotherapy clearly contributes to the development of secondary hematological malignancies but not as clearly to the development of secondary solid tumors. Lung cancer risk is likely increased by chemotherapy,² whereas breast cancer risk appears to be more related to RT than chemotherapy.^{1,13} In several series reporting post-radiation or radiation-associated sarcomas, the most common subtypes have been angiosarcoma, osteosarcoma, fibrosarcoma, and MFH.^{10,15-17} Leiomyosarcoma has not been commonly reported. We were able to find 33 reports of RT associated LMS in the English language literature, comprising 21 single case reports,¹⁸⁻³⁸ four series of two patients^{16,39-41} and one series of four patients.¹⁰ These 33 leiomyosarcomas occurred 6-35 years after therapeutic RT for a variety of benign and malignant diseases. In the largest series, none of the four patients had received chemotherapy, although several other cases have been reported in association with chemotherapy, mostly alkylating agents. The prognosis for patients with post-radiation solid tumors, and sarcomas in particular, is poor.^{16,42,43}

All three of our cases of radiation-associated LMS, which occurred 9-27 years after RT, presented to our clinic in the same month. All had received prior antimetabolite therapy: in two cases 5-fluorouracil, and in one case azathioprine. It is possible that antimetabolite therapy leads to mis-incorporation of nucleotides or other faulty DNA repair in the setting of RT induced sublethal damage, allowing for later sarcomagenesis in otherwise vulnerable smooth muscle cells. Prior reports of secondary sarcomas have not reported the association of antimetabolite therapy as a contributory factor. There is, however, a long latency period from radiotherapy to second primary sarcoma, so the rise in excess cases may lag behind any increase in antimetabolite plus radiotherapy use. With the increasing evidence for the use of 5-FU as a radiosensitizer in the treatment of malignancies, such as head and neck cancer, cervical cancer, stomach cancer, rectal cancer, and pancreatic cancer, more such cases may be seen in the future.

Conclusions

Leiomyosarcoma may rarely occur as a radiation-induced or associated malignancy. In our series of three patients, LMS occurred late after radiotherapy and all had received antimetabolites either concomitant with RT or close to the time of RT. This association has not been previously reported, but there may be a lag time between the increasing use of treatment with RT plus antimetabolite and the development of LMS.

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