Case Report

rare tumors

Rare Tumors
Volume 11: 1–5

DOI: 10.1177/2036361318821763
journals.sagepub.com/home/rtu
SAGE

Neoadjuvant chemotherapy for radiation-associated soft-tissue sarcoma: A case report

Ronak Patel[1], James Hu[2], Shefali Chopra[3] and Christopher Lee[4]

Abstract

Radiation-associated sarcomas are rare and aggressive types of sarcomas that can occur after exposure to ionizing radiation. We examine a case of radiation-associated undifferentiated/unclassified soft-tissue sarcoma with primary disease in the chest wall. The optimal treatment of these patients is surgical resection if possible; however, the role of chemotherapy has not been well defined. The patient described herein had a central tumor in the chest wall. Since many of these patients have borderline resectable tumors, the use of neoadjuvant chemotherapy may be helpful to downstage the tumors for possible surgical resection. In this case, doxorubicin plus ifosfamide chemotherapy was employed with a favorable therapeutic effect prior to being resected. To our knowledge this is the first report of greater than 90% necrosis in a patient with radiation-associated undifferentiated/unclassified soft-tissue sarcoma treated with chemotherapy for a borderline resectable mass.

Keywords

Sarcoma, radiation-induced sarcoma, undifferentiated pleomorphic sarcoma, neoadjuvant chemotherapy sarcoma, radiation sarcoma, radiation-associated sarcoma, radiation-associated, radiation-associated soft-tissue sarcoma

Date received: 14 June 2018; accepted: 6 December 2018

Introduction

With improved local, systemic, and supportive therapies, cancer patients are surviving longer. Such treated patients are at greater risk of secondary malignancies including radiation-associated malignancies. These malignancies are most prevalent in patients treated for breast, lymphoma, head and neck, and gynecologic cancers who have received prior radiation therapy (RT).[1] A small proportion of these secondary malignancies will be diagnosed as sarcoma. The exact origin of radiation-associated sarcomas (RAS) is of some debate, but they are considered to be cancers of mesenchymal origin, and involve cells that can mature into smooth muscle, skeletal muscle, fibrous tissue, bone, cartilage, and blood vessels.[2] RAS can present anywhere from 2 to 57 years after treatment, with a median of 13.6 years, and are characterized by a high mortality rate.[3] They can also present at any site including head and neck, chest, retroperitoneum, pelvis, and extremity. In matched cohort studies, RAS has a worse outcome than primary soft-tissue sarcomas (STS) in terms of 5-year disease-specific survival (44% vs 66%). In addition, central location, achievement of incomplete surgical resection, and lessened use of RT were associated with poorer outcomes in RAS.[4] Since complete surgical resection and central

[1]Internal Medicine, LAC + USC Medical Center, Glendale, CA, USA
[2]Medical Oncology, Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, CA, USA
[3]Pathology, Keck Medical Center, University of Southern California, Los Angeles, CA, USA
[4]Diagnostic Radiology, Keck Medical Center, University of Southern California, Los Angeles, CA, USA

Corresponding author:
Ronak Patel, Internal Medicine, LAC + USC Medical Center, 224 W Dryden St, Apt 116, Glendale, CA 91202, USA.
Email: ronakprakashpatel@gmail.com

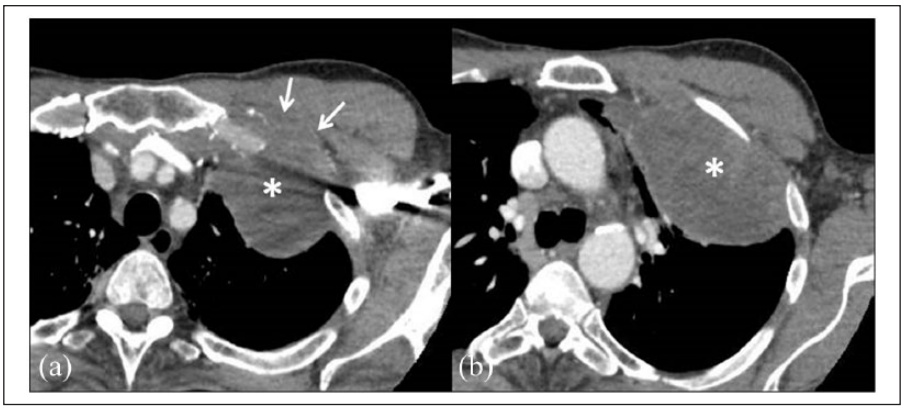

Figure 1. CT chest with contrast, pre-chemotherapy. (a) Superior aortic arch. (b) Carina.
CT chest with contrast at the level of the superior aortic arch (a) and carina (b) prior to treatment demonstrates a large soft tissue mass (asterisk) within the left anterior hemithorax. There is invasion of the mass into the left upper lobe and the superior chest wall (arrows).

location are characteristic of RAS, neoadjuvant chemotherapy with the goal of stabilizing tumor growth and metastasis is an important adjunct to therapy. We report the results and outcome of a patient who presented to our institution with a borderline resectable radiation-associated undifferentiated/unclassified soft-tissue sarcoma (RA-USTS).

Case description

A 58-year-old male diagnosed with Hodgkin's disease 30 years ago received mantle field and para-aortic radiation without chemotherapy. A computed tomography (CT) scan done in August 2015 showed no evidence of disease. In Jan 2017, he presented with left shoulder pain which did not respond to medications and physical therapy. CT showed a large left upper lobe necrotic soft tissue mass protruding through the chest wall between the first and the second ribs with underlying expansion of the left first rib and extension into the pectoral space and neck (Figure 1). The chest wall/lung mass was biopsied via core needle in June and showed spindle cells that immunohistochemically (IHC) stained negative for AE1/AE3, S100, desmin, smooth muscle actin, and CAM 5.2. It was classified as undifferentiated spindle cell sarcoma of at least intermediate grade according to FNCLCC (Figure 2). Neoadjuvant therapy consisting of AIM: adriamycin 75 mg/m^2 and ifosfamide 7500 mg/m^2 with mesna was started. He received two cycles of AIM in July with side effects of anemia requiring transfusion and neutropenia. CT scan in August showed minimal decrease in the size of the tumor (Figure 3). After recovery from his side effects, he was given one dose of liposomal doxorubicin 30 mg/m^2 with plan for surgical resection. He tolerated the liposomal doxorubicin well and on 21 September 2017, he underwent uncomplicated left chest wall resection, left upper lobectomy, and chest wall reconstruction with prolene mesh. He was discharged in good condition without complications. The completely resected specimen showed negative

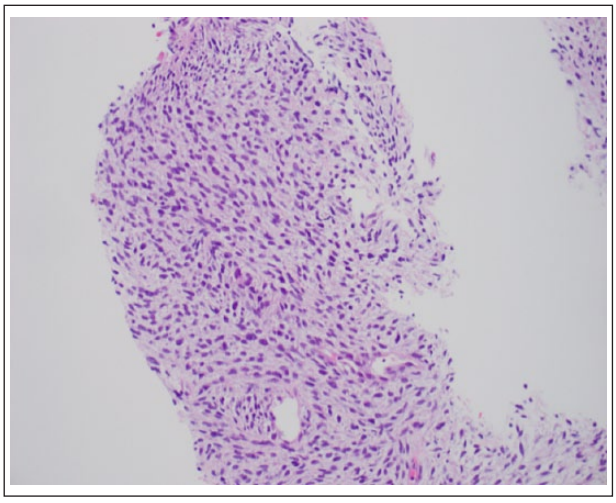

Figure 2. Undifferentiated spindle cell sarcoma. HE stained section; 200×.
Pathology: on the pretreatment needle core biopsy the tumor was composed of spindle cells with a mitotic count of 3/10 HPF. No necrosis was seen on the limited core needle biopsy. IHC stains performed showed the tumor cells to be negative for AE1/AE3, S100, desmin, smooth muscle actin, and CAM 5.2. Given the appearance and the IHC profile, the tumor was best classified as an undifferentiated spindle cell sarcoma, at least intermediate grade based on the FNCLCC grading system.

margins and 95% necrosis within the remaining tumor measuring $9 \times 7 \times 4\,cm^3$ (Figure 4). He reported feeling well until he was admitted on 19 October 2017 for shortness of breath and diagnosed with an ST Elevation Myocardial Infarction which required three drug-eluting stents and a pericardial window for a large effusion. He subsequently underwent cardiac arrest on 29 October 2017 and was on ECMO until he was decannulated on 1 November 2017. He then had a pacemaker placed on 2 November 2017. CT chest on 10 November 2017 showed no evidence of disease. His chest wall mesh from the surgery became infected with

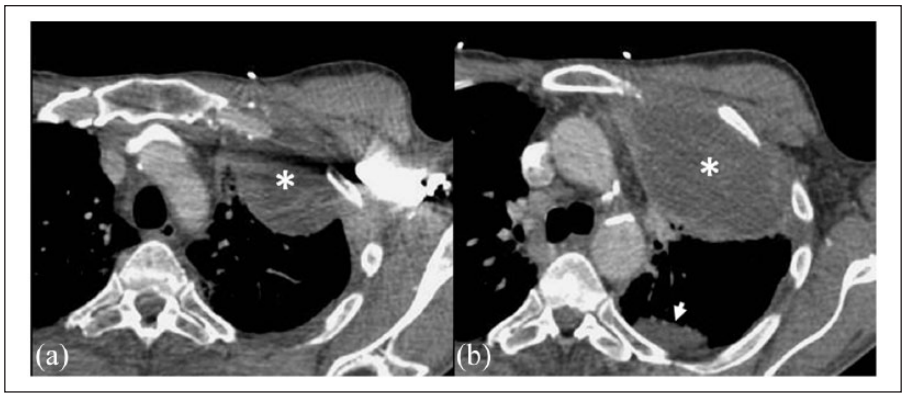

Figure 3. CT chest with contrast, post two cycles of AIM. (a) Superior aortic arch. (b) Carina.
CT chest with contrast at the level of the superior aortic arch (a) and carina (b) following two cycles of AIM again demonstrates a soft tissue mass (asterisk) within the left anterior hemithorax. The mass is not significantly changed in size, but there is relative decreased enhancement reflecting treatment-related necrosis, as well as decreased invasion into the superior chest wall. There has been interval development of a small posteriorly loculated pleural effusion (arrowhead).

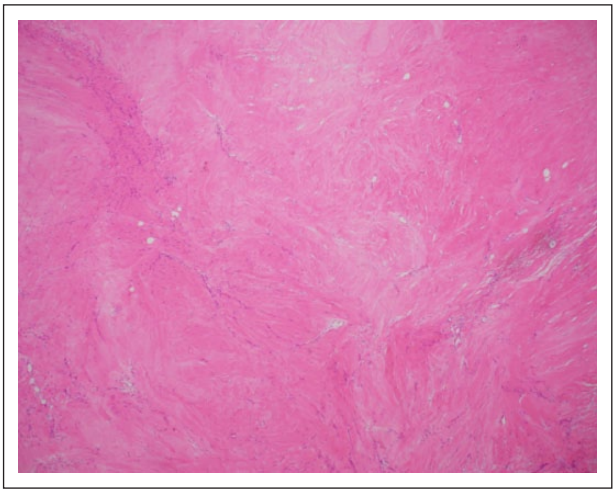

Figure 4. Area of fibrosis with no viable sarcoma seen HE stained section; 100×.
Pathology: on the post treatment, resection specimen there was marked therapy effect with approximately 95% fibrosis and necrosis with very few areas of residual tumor cells.

MDR Pseudomonas which required a mesh explantation on 13 November 2017. Despite maximum ICU care with mechanical ventilation and vasopressors, the patient passed away several months later.

Discussion

Ionizing radiation has been known to be associated with secondary cancers since the early 1800s with RAS first being reported early in the 20th century.[5] Diagnostic criteria for RAS described by Cahan et al.[6] in 1948 included: (1) the development of sarcoma within a radiation field, (2) an asymptomatic interval from the end of radiation to the development of the second malignancy, and (3) the histologic confirmation of a diagnosis of sarcoma from biopsies of the lesion. Currently, RAS account for 3%–5% of all sarcomas and the most common subtype is RA-USTS.[4] Radiation risk for all sarcomas is evident at a dose above 5 Gy with a 10.7-fold increase at doses of 60 Gy or higher.[7] Since RAS are most often high-grade, 5-year survival rates range from 17% to 58% for RAS compared with a much higher 54% to 76% for de novo sarcomas.[4] The current case illustrates the challenges that can be encountered in treating such patients.

Standard of care for RA-USTS involves surgical resection with attempt for clear margins. The benefit of chemotherapy is not clear in these patients, but since many patients have borderline resectable tumors and are at high risk for distant metastases, neoadjuvant systemic therapy may play a role in overall management. Although the response to chemotherapy for RAS is not well known, some authors argue that neoadjuvant systemic therapy for RAS should be dictated by the risk of distant metastasis, especially for sarcomas that are high grade and greater than 5 cm in size.[8] Standard systemic therapy with anthracycline-based chemotherapy is often used alone or in combination for high-grade sarcomas.[9] Standard dose doxorubicin plus intermediate dose ifosfamide was used in this case, but was changed to a more tolerable low-dose liposomal doxorubicin 30 mg/m^2 due to symptomatic arrhythmias from underlying coronary artery disease (CAD). Although there is no demonstrated benefit for use of liposomal doxorubicin in the neoadjuvant setting for sarcoma, there is demonstrated efficacy for the advanced metastatic setting with better tolerability.[10,11]

In the present case, our patient was able to receive a limited number of cycles of chemotherapy prior to undergoing a complete margin negative resection. Our original plan was to give a total of 5 cycles; however our patient passed away from known CAD, which also is a well-documented risk of RT.[12] His cardiac morbidity obviated any protracted use of doxorubicin, but other patients may benefit from additional cycles. This patient was found to have 95% necrosis of his

tumor. The significance of a high percent necrosis has been suggested to be a good prognosticator for survival, but overall the data are still controversial.[8] Of note, CT imaging did not show a significant reduction in size, but this is not unusual in STS as other changes demonstrating therapeutic effect have been described[13] (Figure 3). An effective regimen with a goal of downstaging tumors with neoadjuvant treatment so that surgical resection may be possible, is a reasonable option for those who can tolerate the chemotherapy and with good functional status (ECOG < 2).

The molecular pathogenesis and development of RAS is poorly understood. Earlier studies have implicated DNA aberrations in p53 and Retinoblastoma (Rb) genes.[14] Other research has suggested that radiation-associated carcinogenesis may also be related to the tumor microenviroment as bystander cells often demonstrate chromosomal instability.[2] There has also been a suggestion that RAS are less responsive to chemotherapy than de novo STS. Rumenapp et al.[15] looked at radiation-associated osteosarcomas and found these tumors respond poorly to chemotherapy and are associated with genome-wide loss of heterozygosity. This relative chemoresistance has also been reported by others.[16] Although the response of our current patient could represent a selection bias, we believe that future patients that present with RAS should not be excluded from doxorubicin plus ifosfamide if they can tolerate it. Thus, given the heterogeneity of molecular findings in RAS patients and the dearth of literature on chemotherapy responses, further study is needed to identify patients who might respond to standard chemotherapy.

Conclusion

RAS and cardiac disease are unfortunate long-term consequences for many patients who have undergone RT. This has led to treatments aimed at reducing the use of RT without loss of efficacy; such as in patients with Hodgkin's lymphoma or breast cancer.[17] There is limited data on the effectiveness of systemic treatment in RAS. Since the incidence of RAS will continue to rise, especially with improved therapies and supportive care, management guidelines will be important in managing this unique set of patients who may also suffer from the morbidity of cardiac disease. This is the first reported case to our knowledge of a greater than 90% necrosis in a patient with RA-USTS.

Acknowledgements

We would like to thank Dr Shefali Chopra and Dr Christopher Lee for their help with the pathology and radiology captions, respectively, for the manuscript.

Dr Ronak Patel wrote the first draft of the manuscript. Dr James Hu reviewed and edited the manuscript and approved the final version of the draft.

Conflict of interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

No formal ethical committee was used; all patient identifiers withheld.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Informed consent

Obtained.

Trial registration

Not applicable.

References

1. Brady MS, Gaynor JJ and Brennan MF. Radiation-associated sarcoma of bone and soft tissue. *Arch Surg* 1992; 127(12): 1379–1385.
2. Thiagarajan A and Iyer N. Radiation-induced sarcomas of the head and neck. *World J Clin Oncol* 2014; 5(5): 973–981.
3. Bjerkehagen B, Smeland S, Walberg L, et al. Radiation-induced sarcoma: 25-year experience from the Norwegian Radium Hospital. *Acta Oncol* 2008; 47(8): 1475–1482.
4. Bjerkehagen B, Småstuen MC, Hall KS, et al. Why do patients with radiation-induced sarcomas have a poor sarcoma-related survival? *Br J Cancer* 2012; 106(2): 297–306.
5. Gonzalez AB, Kutsenko A and Rajaraman P. Sarcoma risk after radiation exposure. *Clin Sarcoma Res* 2012; 2(1): 18.
6. Cahan WG, Woodard HQ, Higinbotham NL, et al. Sarcoma arising in irradiated bone: report of eleven cases. 1948. *Cancer* 1998; 82(1): 8–34.
7. Wong F, Boice J Jr, Abramson D, et al. Cancer incidence after retinoblastoma. Radiation dose and sarcoma risk. *Am J Ophthalmol* 1998; 125(2): 1262–1267.
8. Patel SR. Radiation-induced sarcoma. *Curr Treat Opt Oncol* 2000; 1(3): 258–261.
9. Rawat S. Radiation induced sarcomas in head and neck, https://www.slideshare.net/shehrawat/radiation-induced-sarcomas-in-head-and-neck (accessed 17 September 2011).
10. O'Shaughnessy JA. Pegylated liposomal doxorubicin in the treatment of breast cancer. *Clin Breast Cancer* 2003; 4(5): 318–328.
11. Xing M, Yan F, Yu S, et al. Efficacy and cardiotoxicity of liposomal doxorubicin-based chemotherapy in advanced breast cancer: a meta-analysis of ten randomized controlled trials. *PLoS ONE* 2015; 10(7): e0133569.
12. Borges N and Kapadia SR. Radiation-induced CAD: incidence, diagnosis, and management outcomes, https://www.acc.org/latest-in-cardiology/articles/2018/05/24/01/44/radiation-induced-cad (accessed 21 September 2018).
13. Lucasa DR, Kshirsagara MP, Biermannb JS, et al. Histologic alterations from neoadjuvant chemotherapy in high-grade

extremity soft tissue sarcoma: clinicopathological correlation, http://theoncologist.alphamedpress.org/content/13/4/451.full.html (accessed 1 April 2008).
14. Brachman DG, Hallahan DE, Beckett MA, et al. P53 gene mutations and abnormal retinoblastoma protein in radiation-induced human sarcomas. *J Cancer Res* 1991; 51(23): 6393–6396.
15. Rumenapp C, Smida J, Gonzalez-Vasconcellos I, et al. Secondary radiation-induced bone tumours demonstrate a high degree of genomic instability predictive of a poor prognosis. *Curr Genom* 2012; 13(6): 433–437.
16. Dineen SP, Roland CL, Feig R, et al. Radiation-associated undifferentiated pleomorphic sarcoma is associated with worse clinical outcomes than sporadic lesions. *Ann Surg Oncol* 2015; 22(12): 3913–3920.
17. National Comprehensive Cancer Network. Breast cancer (version 1.2018), https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf (accessed 21 September 2018).