Case Report
Volume 7:2, 2023

Clinical and Medical Case Reports

ISSN: 2684-4915 **Open Access**

Cardiac Angiosarcoma after Chemo-Radiotherapy for Non-Hodgkin's Lymphoma: A Case Report and Review of Literature

M. Troiano[1]*, E. E. Piazzolla[1], S. Cossa[1], A. Raguso[1], I. Troiano[1], P. Corsa[1], T. Munafò[1], F.P. Ricci[1], A. Parisi[2], F. Colangelo[3] and S. Parisi[1]

[1]IRCCS "Casa Sollievo della Sofferenza", Radiation Oncology Department, San Giovanni Rotondo, Italy

[2]Department of Oncology, Marche Polythecnic University, Marche University Hospital, Ancona, Italy

[3]Radiation Oncology Department, San Gerardo Hospital-University of Milan-Bicocca, Monza, Italy

Abstract

Sarcomas in irradiated tissues are often considered second cancers and, among these, Angiosarcoma (AS) is an aggressive, malignant endothelial-cell tumour of vascular or lymphatic origin. AS can arise in any site of the body, but it very rarely occurs in major blood vessels or in the heart.

We report the case of 51-year old woman who developed a cardiac AS 20 year after chemoradiation therapy for bulky non-Hodgkin's disease.

She was healthy until December 2013 when, because of persistent dyspnea, the family physician prescribed an echocardiographic exam that evidenced an intracavitary left atrial mass that caused functional severe mitral stenosis. After complete surgical excision, the mass was confirmed to be high grade AS. No residual tumor was detected by a post-operative cardiac magnetic resonance (MRI) and a positron emission tomography (PET) scan didn't show images of neoplastic masses in other sites.

The patient was treated with adjuvant chemotherapy. She died 27 months after diagnosis.

Keywords: Angiosarcoma • Radiotherapy

Introduction

Malignant primary cardiac neoplasms account for about 10% of all primary cardiac neoplasms. Most of malignant primary cardiac neoplasms are sarcomas, 76% of which being angiosarcomas (AS). These, in about one-third of cases, are poorly differentiated [1]. The most frequent site of cardiac ASs is the right atrium.

This kind of neoplasm is very aggressive and has a high propensity for invasiveness; in fact, it is often associated with cardiac tamponade, pericardial constriction, lung, bone, liver and spleen metastasis and, consequently, a very poor prognosis [2].

In terms of treatments, radical excision appears to be the most effective treatment with a median survival of 14 months [3].

The 20 year single-institution retrospective case-series by Look HNJ, et al. reports a median OS of 17 months for patients who underwent surgical resection, and 5 months for non-resected groups, confirming the poor prognosis of cardiac AS [4].

Low expression levels of Ki-67 and adjuvant chemotherapy are important prognostic factors because they tend to be associated with long-term survival for cardiac sarcomas [5].

A case-report by Fukunaga N, et al. [2] described the case of a patient treated with adjuvant radiochemotherapy who died from liver metastasis more than three years after diagnosis.

In a case-series by Wu Y, et al. on 12 patients [6], postoperative chemotherapy and radiotherapy (RT) tended to improve OS for cardiac sarcoma; however, despite the availability of several sizeable studies, data on the adjuvant setting are still limited.

Although the use of adjuvant therapies is still debated, their use is recommended because they reduce the possibility of metastasis with this highly invasive disease [7].

However, RT, both exclusive and adjuvant, is difficult to apply due to respiratory movement and heartbeat; moreover, it carries an increased risk of damage of the surrounding tissues and of RT-related cardiac toxicity [8]. Some opportunities to optimize the delivered dose to the target while sparing healthy tissues is given by the application of apnea techniques, respiratory gating, real-time tumor tracking, IMRT and 4D tumor motion analysis.

Interestingly, for patients unfit for surgery, helical tomotherapy at radical doses (60 Gy) has proved to provide good outcomes [9].

In patients who received RT, the main risk factors are: combined modality treatment with cytotoxic drugs, a large irradiation field, younger age and radiation dose.

The relationship between secondary cancers and previous RT treatment is well known. Secondary neoplasms following chemotherapy and RT for both Hodgkin's lymphoma and non-Hodgkin's lymphoma have been described.

Case Presentation

We report the case of 51-year-old woman who developed a cardiac AS 20

***Address for Correspondence:** M. Troiano, IRCCS "Casa Sollievo della Sofferenza", Radiation Oncology Department, San Giovanni Rotondo, Italy, E-mail: ippotroiano88@gmail.com*

Received: 26 March, 2023, Manuscript No. cmcr-23-92926; **Editor assigned:** 28 March, 2023, Pre QC No. P-92926; **Reviewed:** 08 April, 2023, QC No. Q-92926; **Revised:** 13 April, 2023, Manuscript No. R-92926; **Published:** 28 April, 2023, DOI: 10.37421/2684-4915.2023.7.250

years after chemoradiation for bulky non-Hodgkin's disease.

In December 2013, the patient presented at our Institution with severe and worsening dyspnea. Echocardiogram showed a left atrial mass which involved a portion of the left atrium wall and the middle segment of the anterior mitral leaflet, causing severe mitral stenosis. Computed tomography (CT) scans of the chest, the abdomen and the pelvis confirmed the presence of a left atrial mass with pericardial and pleural effusion without any evidence of distant metastases.

Because of the severity of the clinical picture, it was not possible to make additional imaging examinations. The patient was quickly sent to surgery for complete removal of the mass. The histologic exam showed a high-grade epitelioid AS and revealed that the immunohistochemical analysis was positive for CD31,CD34 and CK pool and negative for EMA.

About 20 years earlier, in 1992, the patient was treated in our Institution with chemoradiation therapy for bulky non-Hodgkin's disease of the mediastinum (T- Cell Lymphoblastic Lymphoma, IIA stage).

The chemotherapy scheme used was LSA2 L2, a protocol for the treatment of childhood non-Hodgkin's lymphoma that included an induction phase with cyclophosphamide, daunomycin, vincristine, prednisone and intrathecal (IT) methotrexate; a consolidation phase with cytarabine, thioguanine, L-asparaginase, carmustine and IT methotrexate; and a maintenance phase that included thioguanine, cyclophosphamide, hydroxyurea, daunorubicin, both oral and IT methotrexate, and vincristine. The radiation therapy was administered in supine position with 8MV photon beams by anteroposterior/posteroanterior (AP/PA) fields (Figure 1).

The Clinical Target Volume (CTV) consisted of the bulky disease at the time of diagnosis (all mediastinum) and was treated to a total dose of 24 Gy (2 Gy/fraction). After that schedule, the CTV was reduced to residual mediastinal mass and reached a total dose of 36 Gy with the same fraction. The treatments were well-tolerated and, some months later, the patient underwent autologous bone marrow transplantation (ASCT) after conditioning regimen based on chemotherapy with busulfan, etoposide and cyclophosphamide.

Approximately one month after bone marrow transplantation, she received whole brain RT for a total dose of 24 Gy (180 cGy/fraction) as central nervous system (CNS) prophylaxis (according to the treatment protocol for high risk lymphomas). The patient received an appropriate follow-up with no signs of recurrence.

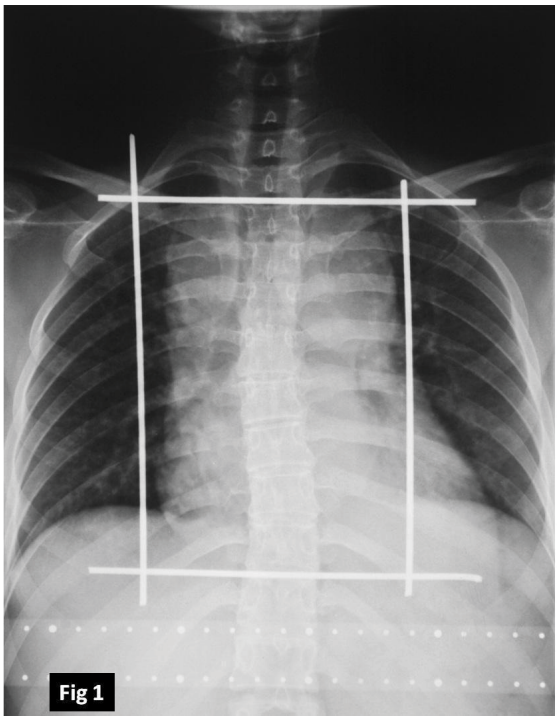

Figure 1. RT field for previous non-Hodgkin lymphoma radiotherapy.

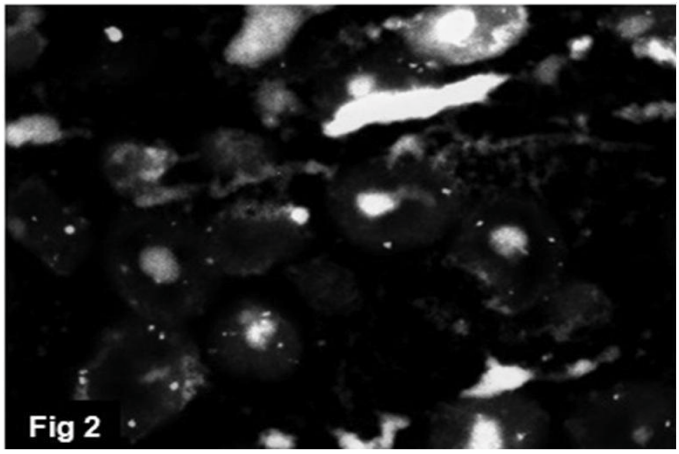

Figure 2. C-myc amplification (Abbot Vysis LSI IGH/MYC, CEP 8 tri color, dual fusion).

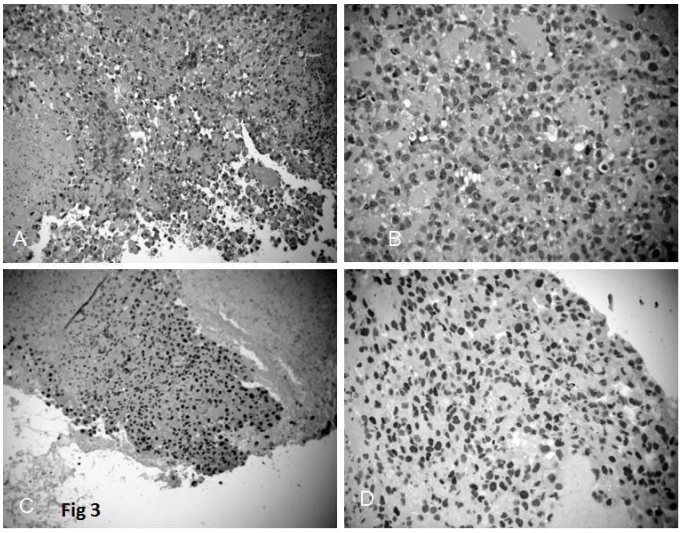

Figure 3. (A) Angiosarcoma EE 10X, **(B)** Angiosarcoma EE 20X, **(C)** Angiosarcoma IIC Ab c-myc 10X and **(D)** Angiosarcoma IIC Ab c-myc 20X.

Table 1. Cases of cardiac AS after radiation therapy.

Cases of Cardiac AS after Radiation Therapy					
Reference	**Pt Sex, Age, Original Malignancy**	**Irradiation Field**	**Latency Period after Irradiation(yr)**	**Treatment**	**Outcome**
Killion MJ, et al [26]	M, 54, seminoma	Supraclavicular areas and mediastinum	15	Pericardiectomy Post-op CT	Died 3-4 mo after onset of symptoms
Sharma A, et al [27]	F, 41, breast cancer	Left mediastinum	8	Pericardiectomy Post-op CT	Palliative treatment
Current case	F,51, lymphoma non-Hodgkin	Mediastinum	20	Radical surgical excision of left atrial mass Post-op CT	Died 27 mo after diagnosis

In December 2013, after the diagnosis of left atrial AS and after cardiac surgery, positron-emission tomography (PET) and cardiac magnetic resonance (MR) showed no evidence of metastases and no presence of heart sarcoma.

The patient was treated with adjuvant chemotherapy (taxol for four cycles and gemcitabine for two cycles). However, she died from heart failure 27 months after the diagnosis of cardiac AS.

Discussion and Conclusion

AS is a very rare sarcoma of vascular or lymphatic origin.

About 2% of soft tissue sarcomas and 4-5% of cutaneous soft tissue sarcomas are AS and are divided into cutaneous AS, lymphoedema-associated AS, radiation-induced AS, primary breast AS and soft tissue AS [10].

In a 2019 review [11] on 65 patients with non-metastatic AS, of whom 29.2% had received RT previously, the median follow-up in patients with primary AS was 22.6 months *vs.* 14.8 months in patients with RT-related AS. The latter had worse outcomes than primary AS with respect to locoregional control and OS, which is consistent with the survival results reported in the studies by Yin M, et al. [12].

The most frequently reported RT-related ASs involves superficial soft tissues and present as bluish or purple nodules with purple discoloration [13]. This type of AS may develop in the irradiated chest wall after mastectomy or in the residual breast after breast-conserving therapy, with a median interval of 10 years from RT [14]; however, the latency time is still not perfectly known.

Lyou Y, et al. review reports an incidence of 0.9 cases per 1000 for RT-related breast AS, with onset up to 23 years after therapies [15].

The first case of postmastectomy AS was reported by Stewart and Treves in 1948 [16].

While wide resection with negative margin remains the primary therapy, this type of disease can also be approached with alternative techniques, such as electrochemotherapy [17].

Non-cutaneous AS is less frequently reported, with a very poor cure rate [18].

AS can arise in any site of the body, but it very rarely occurs in major blood vessels or in the heart. There are few reports of malignant transformation of benign vascular lesions [19]. Well described risk factors exist such as chronic lymphoedema, various chemicals (vinyl chloride, thorium dioxide, arsenic, anabolic steroids), foreign bodies, some familial syndromes (neurofibromatosis NF-1; mutations of BRCA 1 or BRCA 2 genes, Maffucci Syndrome). Radiation therapy is an independent risk factor [10].

According to Nascimento AF, et al. [20], RT-related AS is usually considered as a high grade tumor, regardless of morphology, with the highest metastatic potential among sarcomas.

Cahan WG, et al. [21] and later Murray EM, et al. [22] defined some diagnostic criteria for radiation-induced sarcomas: a history of exposure to radiation, no prior sarcomas, and different histologic features from those of the primary tumor, latent period after RT.

We believe that our case meets these criteria because the patient did not have a history of sarcoma and because she received radiation therapy approximately 20 years before the development of the sarcoma, histologically confirmed.

From a molecular point of view, despite their identical morphology, secondary AS is different from primary AS and from atypical vascular lesions (AVL) arising in the irradiated tissue. It has recently been demonstrated that radiation-induced ASs are characterized by high amplification of the c-myc oncogene, which is less observed in primary AS, in radiation-induced sarcomas with non-AS morphology and in radiation-induced AVL [23].

C-myc is a proto-oncogene that encodes a transcription factor involved in cell growth, proliferation, apoptosis and other cancer processes such as angiogenesis [23]. The consequences of myc amplification are not yet clear. Probably it does not influence the tumour cell morphology and turnover or the disease prognosis, but it is often linked to high tumour grade such as malignant fibrous histiocytoma of the bone, high grade chondrosarcoma, osteosarcoma [24].

Recently, an excellent immunohistochemical (IHC) and fluorescence *in situ* hybridization (FISH) concordance in secondary mammary AS was found, but this concordance seems to be poor in ASs of non-mammary sites [23].

Our Pathology Unit studied the myc protein expression (IHC analysis) and the myc amplification (FISH analysis) in the surgical specimens of our case: they found myc amplification and concordance between IHC and FISH (Figures 2 and 3).

It was observed that inactivation of myc can change the malignant phenotype of rhabdomiosarcomas and cause regression in osteosarcoma cells [24]. These observations raise the possibility that specific manipulation of myc may be an effective therapeutic strategy for selected sarcomas including secondary AS.

Moreover, because AS is an endothelial cell tumor, lots of studies have investigated the key role of angiogenesis in this particular type of sarcoma: the expression of vascular epithelial growth factor receptor (VEGFR) 1 and 2 was found on AS cells cultured on coverslips [25-27]. Thus, the inhibition of the VEGF/VEGFR pathway could be an effective therapy for this tumor. To our knowledge, this case report is the third case of AS after radiochemotherapy reported in the literature (Table 1).

In conclusion, cardiac AS represents a very rare entity and tends to occur in younger patients (67.1% at age younger than 54). It often presents as a metastatic neoplasm due to hematogenous spread. Consequently, surgery is not always the primary treatment option, although it is the therapy of choice for localized AS and primary AS. Cardiac transplantation may be another option, although its role is yet to be confirmed [28].

The behavior of secondary AS is remarkably similar to the primary, with a median survival period of 14.5-34 months and a 5-year survival rate of approximately 35% [29].

One possible way is neoadjuvant chemotherapy. Indeed, Saleh WKA, et al. showed a higher R0 resection rate (47 *vs.* 33%) and a better OS (20 *vs.* 9.5 months, p=0.417) for right-side cardiac sarcomas (68% were AS), regardless of the metastatic status [30].

In terms of local control, the multimodal therapy is certainly the best approach [11].

The causes of cardiac AS are still a matter of debate. Some have been related to previous RT; thus, the increased overall survival after cancer makes it necessary to assess the incidence of secondary cancers in irradiated patients.

References

1. Ambrus, Nóra, Kálmán Havasi, Anita Kalapos and László Sághy, et al. "Primary cardiac angiosarcoma: A case report." *Echocardiography* 35 (2018): 267-271.
2. Fukunaga, Naoto, Takeshi Kitai, Yukihiro Imai and Yutaka Furukawa, et al. "Three-year survival in primary cardiac angiosarcoma." *J Med Invest* 64 (2017): 181-183.
3. Antonuzzo, L., V. Rotella, F. Mazzoni and L. Doni, et al. "Primary cardiac angiosarcoma: A fatal disease." *Case Rep Med* 2009 (2009).
4. Look Hong, Nicole J., Prakash K. Pandalai, Jason L. Hornick and Prem S. Shekar, et al. "Cardiac angiosarcoma management and outcomes: 20-year single-institution experience." *Ann Surg Oncol* 19 (2012): 2707-2715.
5. Aboud, Anas, Kassar Farha, Wan Chin Hsieh and Frank Brasch, et al. "Prognostic factors for long-term survival after surgical resection of primary cardiac sarcoma." *Thorac Cardiovasc Surg* 67 (2019): 665-671.
6. Wu, Yufan, Lynn Million, Everett J. Moding and Gregory Scott, et al. "The impact of postoperative therapy on primary cardiac sarcoma." *J Thorac Cardiovasc Surg* 156 (2018): 2194-2203.
7. Wang, Meng, Ganglan Fu, Huiqi Jiang and Kuan Zeng, et al. "Multimodality treatment for cardiac angiosarcoma." *Intern Med* 53 (2014): 1949-1953.
8. Luo, Limin, Weipeng Zhao, Yongshi Wang and Kun Liu. "Cardiac angiosarcoma: A case report and review of the literature." *Echocardiography* 38 (2021): 2083-2090.
9. Franceschini, Davide, Vieri Scotti, Gabriele Simontacchi and Icro Meattini, et al. "Application of helical tomotherapy for the treatment of a right atrium angiosarcoma: A case report." *Tumori* 99 (2013): e233-e236.
10. Young, Robin J., Nicola J. Brown, Malcolm W. Reed and David Hughes, et al.

"Angiosarcoma." *The lancet oncology* 11 (2010): 983-991.

11. Merfeld, E., P. Gabani, M. B. Spraker and I. Zoberi, et al. "Clinical outcomes and prognostic features of angiosarcoma: Significance of prior radiation therapy." *Clin Oncol* 31 (2019): 232-241.
12. Yin, Ming, Wenge Wang, Joseph J. Drabick and Harvey A. Harold. "Prognosis and treatment of non-metastatic primary and secondary breast angiosarcoma: A comparative study." *BMC cancer* 17 (2017): 1-8.
13. Cafiero, Ferdinando, Marco Gipponi, Alberto Peressini and Paola Queirolo, et al. "Radiation-associated angiosarcoma: Diagnostic and therapeutic implications—Two case reports and a review of the literature." *Cancer: Interdisciplinary International Journal of the American Cancer Society* 77 (1996): 2496-2502.
14. Gladdy, Rebecca A., Li-Xuan Qin, Nicole Moraco and Mark A. Edgar, et al. "Do radiation-associated soft tissue sarcomas have the same prognosis as sporadic soft tissue sarcomas?." *J Clin Oncol* 28 (2010): 2064-2069.
15. Lyou, Yung, Emily Barber, Rita Mehta and Thomas Lee, et al. "Radiation-associated angiosarcoma of the breast: A case report and literature review." *Case Rep Oncol* 11 (2018): 216-220.
16. Stewart, Fred W. and Norman Treves. "Lymphangiosarcoma in postmastectomy lymphedema. A report of six cases in elephantiasis chirurgica." *Cancer* 1 (1948): 64-81.
17. Cencelj-Arnez, Romi, Jerica Novak, Andreja Klevisar Ivancic and Masa Bosnjak, et al. "Radiotherapy-associated angiosarcoma in the breast reconstructed by autologous free-flap and treated with electrochemotherapy." *Radiol Oncol* 55 (2021): 77-81.
18. Csaba, Polgár, Orosz Zsolt, Szerdahelyi Andrea and Fodor János, et al. "Mellkasfali és emlô angiosarcoma sugárkezelés után: A radiogén eredet, a diagnózis és a kezelés kérdései." *Magyar Onkológia* 44 (2000).
19. Scalea, Joseph R., Branko Bojovic, Robin Legros and Julia Choi, et al. "Angiosarcoma following radiation therapy for breast cancer: Case presentation and clinical management considerations." *Open J Path* 3 (2013): 180.
20. Nascimento, Alessandra F., Chandrajit P. Raut and Christopher DM Fletcher. "Primary angiosarcoma of the breast: Clinicopathologic analysis of 49 cases, suggesting that grade is not prognostic." *Am J Surg Pathol* 32 (2008): 1896-1904.
21. Cahan, William G., Helen Q. Woodard, Norman L. Higinbotham and Fred W. Stewart, et al. "Sarcoma in irradiated bone. Report of eleven cases." *Cancer* 1 (1948): 3-29.
22. Murray, Elizabeth M., Dudley Werner, Elizabeth A. Greeff and Deryck A. Taylor. "Postradiation sarcomas: 20 cases and a literature review." *Int J Radiat Oncol Biol Phys* 45 (1999): 951-961.
23. Ginter, Paula S., Juan Miguel Mosquera, Theresa Y. MacDonald and Timothy M. D'Alfonso, et al. "Diagnostic utility of MYC amplification and anti-MYC immunohistochemistry in atypical vascular lesions, primary or radiation-induced mammary angiosarcomas and primary angiosarcomas of other sites." *Hum Pathol* 45 (2014): 709-716.
24. Manner, Johanna, Bernhard Radlwimmer, Peter Hohenberger and Katharina Mössinger, et al. "MYC high level gene amplification is a distinctive feature of angiosarcomas after irradiation or chronic lymphedema." *Am J Pathol* 176 (2010): 34-39.
25. Azzariti, Amalia, Letizia Porcelli, Anita Mangia and Concetta Saponaro, et al. "Irradiation-induced angiosarcoma and anti-angiogenic therapy: A therapeutic hope?." *Exp Cell Res* 321 (2014): 240-247.
26. Killion, Matthew J., Harvey S. Brodovsky and Roland Schwarting. "Pericardial angiosarcoma after mediastinal irradiation for seminoma: A case report and a review of the literature." *Cancer: Interdisciplinary International Journal of the American Cancer Society* 78 (1996): 912-917.
27. Sharma, Ashwini, Patrick A. DeValeria, Robyn M. Scherber and Gavin Sugrue, et al. "Angiosarcoma causing cardiac constriction late after radiation therapy for breast carcinoma." *Tex Heart Inst J* 43 (2016): 81.
28. Chen, Tom Wei-Wu, Jessica Burns, Robin L. Jones and Paul H. Huang. "Optimal clinical management and the molecular biology of angiosarcomas." *Cancers* 12 (2020): 3321.
29. Goldust, Mohamad, Mario Giulini, Beate Weidenthaler-Barth and Mrinal Gupta, et al. "Increased risk of angiosarcoma secondary to cancer radiotherapy: Case series and review of the treatment options." *Dermatol Ther* 33 (2020): e13234.
30. Saleh, Walid K. Abu, Basel Ramlawi, Oz M. Shapira and Odeaa Al Jabbari, et al. "Improved outcomes with the evolution of a neoadjuvant chemotherapy approach to right heart sarcoma." *Ann Thorac Surg* 104 (2017): 90-96.

How to cite this article: Troiano, M, E. E. Piazzolla, S. Cossa and A. Raguso, et al. "Cardiac Angiosarcoma after Chemo-Radiotherapy for Non-Hodgkin's Lymphoma: A Case Report and Review of Literature." *Clin Med Case Rep* 7 (2023): 250.