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CASE REPORT

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Radiation-induced angiosarcoma—An unusual cause of recurrent pleural effusion

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Abstract

Although rare, radiotherapy can induce secondary malignancies, such as radiation-induced angiosarcoma (RIAS), which is associated with a poor prognosis. Early detection is crucial for improving outcomes. The modified Cahan criteria are instrumental in diagnosing RIAS, which is ultimately confirmed through histological examination. We present a case of a middle-aged woman who developed RIAS after undergoing radiotherapy post-surgery and adjuvant chemotherapy for right-sided breast cancer. The patient presented with a rapidly reaccumulating right-sided pleural effusion, and RIAS was confirmed through pleural biopsy and aspirate. This case report highlights the pathway for establishing a diagnosis of RIAS and the need for early detection through clinical examination and surveillance imaging for patients following radiotherapy.

KEYWORDS
angiosarcoma, breast cancer, pleural effusion, radiation therapy

INTRODUCTION

Secondary malignancy is malignancies are a rare but serious complication of radiotherapy, with exact incidence rates not well established. RIAS often presents with non-specific cutaneous symptoms such as eczematous rash or purplish-red nodules in or around the previous radiation field,[1,2] which can complicate and delay diagnosis. Given its poor prognosis, early detection is crucial. The modified Cahan criteria can assist in diagnosing RIAS,[3,4], and the diagnosis is confirmed via histology of pleural biopsy.

CASE REPORT

A 54-year-old female with stage IIA (pT2N1a) HR + HER2- right-sided breast cancer initially underwent mastectomy and lymph node dissection, followed by four cycles of adjuvant chemotherapy with docetaxel and cyclophosphamide, and radiotherapy with a total radiation dose of 50 Gy. Subsequently, she commenced adjuvant tamoxifen. Four years later, she underwent mastopexy and an implant-based reconstruction.

Eight years after the initial breast cancer diagnosis, she presented with a 4–6-week history of exertional dyspnoea, pleuritic chest pain and 1 kg weight loss. Physical examination revealed stony dullness to percussion over the right lower chest with reduced breath sounds. Imaging showed a large right-sided pleural effusion requiring drainage. The patient underwent drainage of the right-sided pleural effusion, and a chest x-ray post-procedure confirmed complete resolution. However,

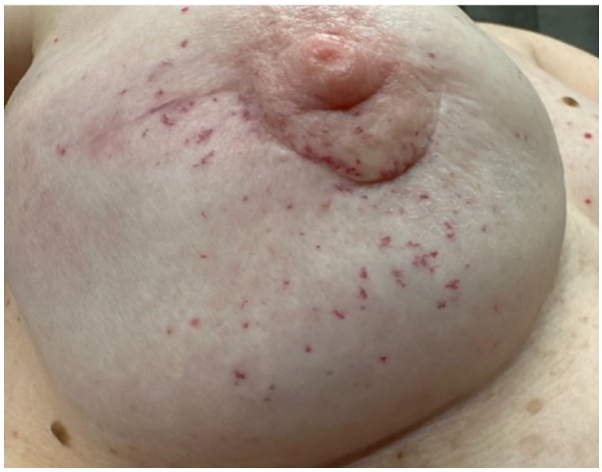

FIGURE 1 Telangiectatic rash over right breast.

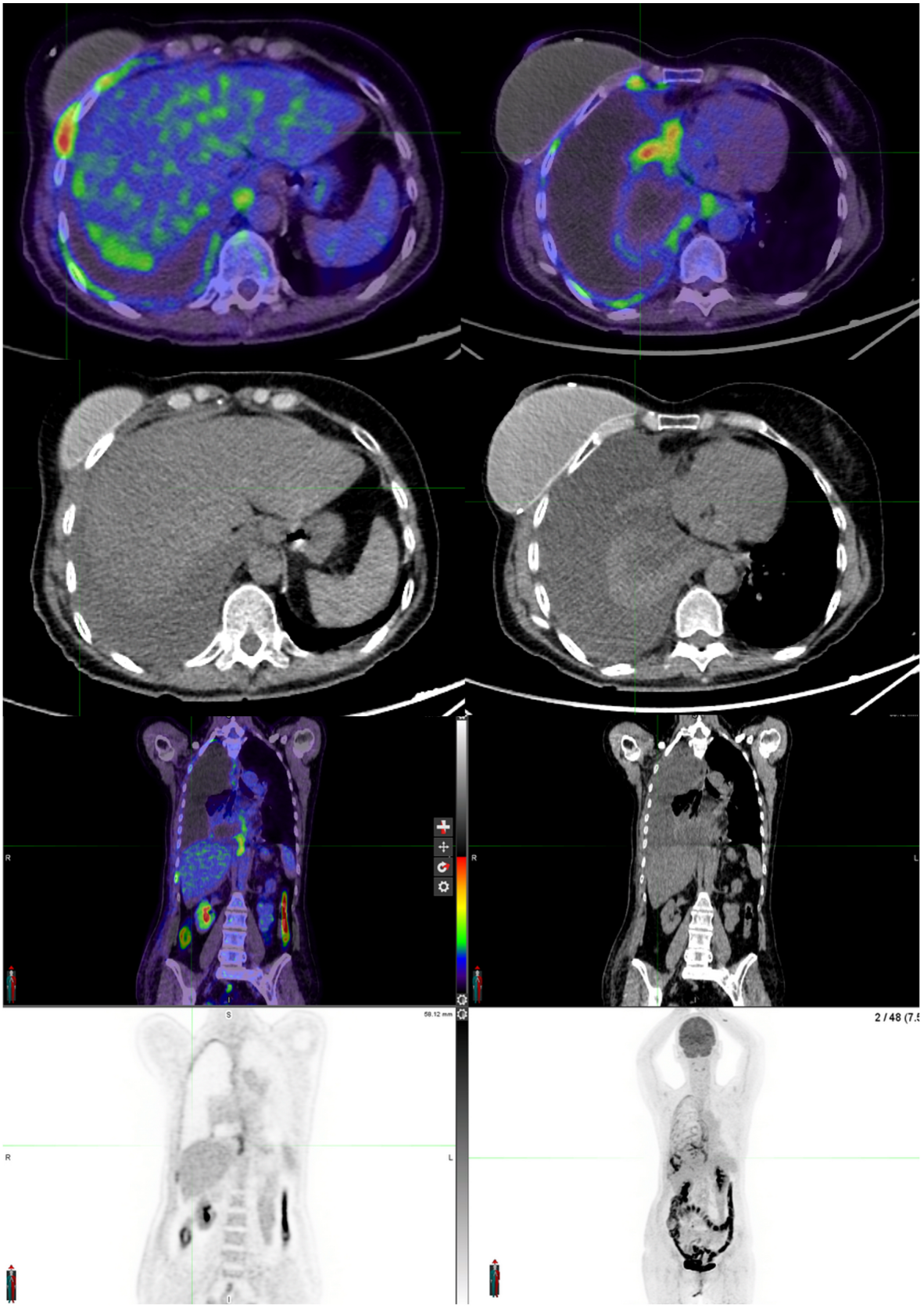

FIGURE 2 Positron emission tomography (PET)-computed tomography (CT) of the chest demonstrating [18FDG] flurodeoxyglucose–avid areas within inferolateral aspect of right breast implant and avid right pleural involvement and effusion.

she returned 6 days later with recurrent symptoms and signs of fluid reaccumulation, so the patient was admitted for further investigations and management. Further examination revealed a telangiectatic rash over the right breast (Figure 1). Laboratory investigations, including full blood examination, urea, creatinine and electrolytes, liver function tests, troponin, C-reactive protein, blood and urine culture and rapid SARS-CoV2 antigen test were unremarkable. Chest computed tomography (CT) showed a recurrent right-sided pleural fluid collection with complete collapse of the right lower and middle lobes. Positron Emission Tomography-CT demonstrated an active lesion within the inferolateral aspect of right breast implant and avid right pleural involvement (Figure 2). Pleural fluid aspiration confirmed malignancy, with cells positive for ERG, D2-40, CD31 and negative for GATA3, ER, PR, HER2, CK20, CK7, CD20, CK5/6, WT1, cytokeratin, p40, S100, SOX10. Pleural biopsy demonstrated proliferation of epithelioid and spindle cells with areas of haemorrhage and necrosis (Figure 3A,B). Immunostaining identified atypical cells positive for ERG (Figure 3C), CD31, M2-A but negative to CD34, HHV8, AE1/3, cam 5.3, mesothelin, WT-1, calretinin. With the patient's clinical history of previous radiotherapy to the right chest (Figure 4) and the presence of a telangiectatic rash within irradiated field, combined with the absence of asbestos exposure and the immunostaining patterns, a diagnosis of RIAS involving the pleura was established.

She had ongoing reaccumulation of pleural fluid throughout her admission, requiring drainage up to 3 litres within a week and subsequently underwent video-assisted pleurodesis. Despite this, she required a PleurX draining catheter 2 weeks later due to rapid reaccumulation. Shortly thereafter she commenced first line palliative intent therapy with weekly paclitaxel. Somatic tumour sequencing (TSO 500) yielded no actionable mutations.

Patient remained clinically stable, with no respiratory symptoms on paclitaxel for approximately 10 months except for a brief interruption due to a febrile illness. Disease progression was demonstrated on routine restaging FDG-PET with increasing pleural nodularity and thickening. Second-line chemotherapy with liposomal doxorubicin was commenced, with an excellent clinical and radiological response and complete metabolic response on FDG-PET. Six months later, she entered a phase-1 clinical trial (NCT06082960) due to oligoprogression, but withdrew consent due to symptomatic progression in the chest wall, necessitating opiate analgesia. Restaging imaging demonstrated progressive disease in the retrosternum, and clinically symptomatic disease with a right paravertebral T9-11 mass. At the time of writing, she had resumed liposomal doxorubicin after completing palliative radiotherapy (total 25 Gy) to the paravertebral mass.

DISCUSSION

Radiotherapy can induce secondary malignant neoplasms, such as soft tissue sarcoma, and occurs only in 0.03% to 0.2% of post-irradiation follow-up over a 10-year period.[5]

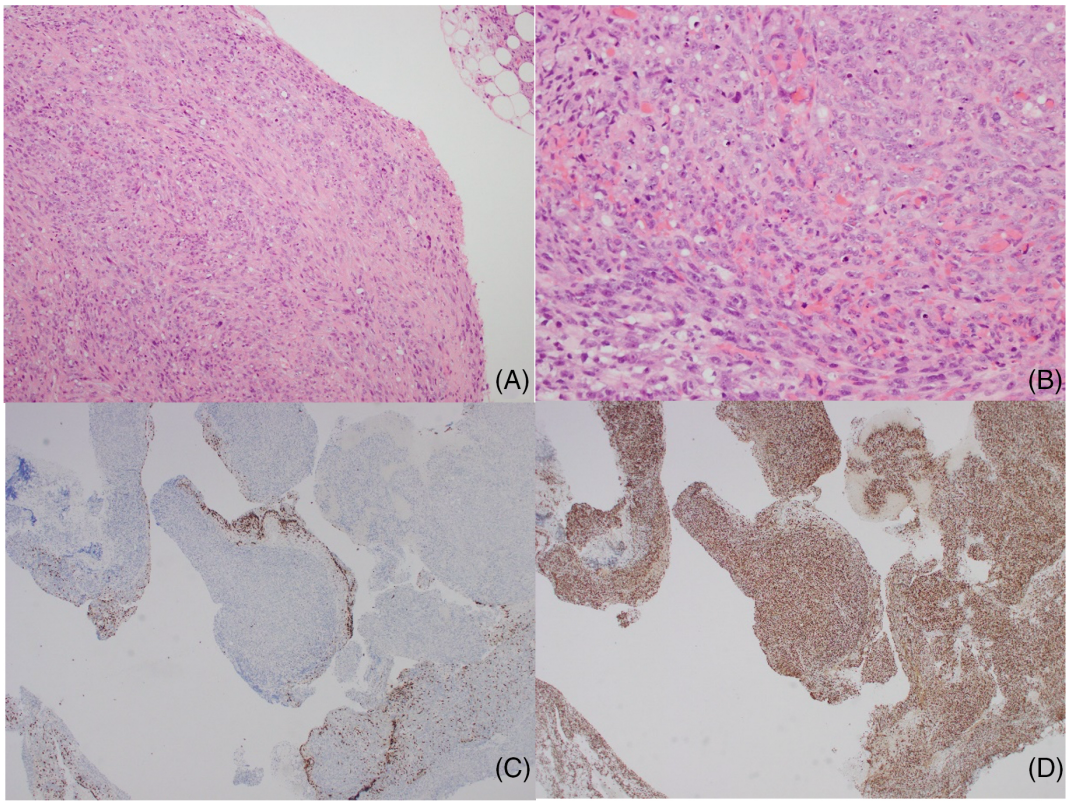

FIGURE 3 Pleural biopsy (A): H&E ×10 (B): H&E ×20 (C): Atypical cells ERG+ ×2 (D): Mesothelial cells AE1/3 + ×2.

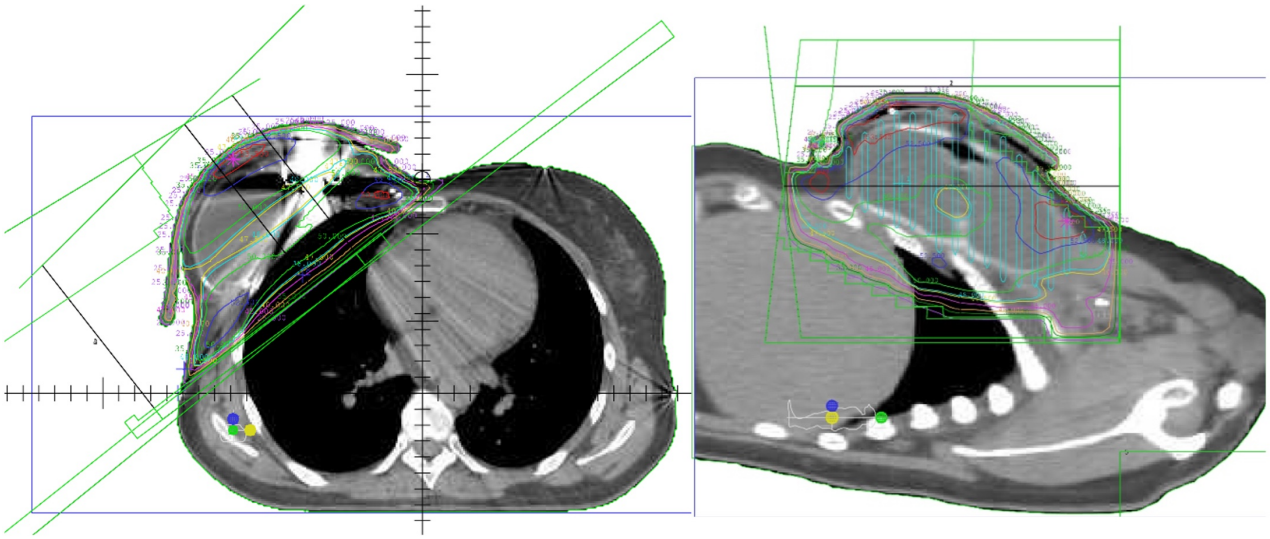

FIGURE 4 Radiotherapy treatment planning.

TABLE 1 Literature review of RIAS cases involving the pleura.

Case	MILLER[8]	OGINO[9]	Our case
Age, Sex	75 M	67 M	54F
Presentation	SOB and recurrent pleural effusion	Fever and SOB	SOBpleuritic chest pain recurrent pleural effusion
Primary tumour	Stage IIIA left upper lobe poorly differentiated SCC	Left mandibular gingival SCC	Stage IIA right sided breast cancer
Total radiation dose	60 Gy	60 Gy	50 Gy
Latency to diagnosis of RIAS since RT	4 years	8 years	8 years
PET	Increased 18FDG avidity along the middle to upper right pleural surface with no other avid lesions	Increased 18FDG activity in left neck field and left apical portion of the thoracic wall	Increased 18FDG avidity within inferolateral aspect of right breast implant and avid right pleura involvement and effusion
Histopathology	Proliferation of a mixture of epithelioid and spindle cell features and marked nuclear pleomorphism with mitotic figures and prominent nucleoli	Proliferation of malignant tumour cells with acidophilic cytoplasm and loose cell–cell adhesion.	Proliferation of epithelioid and spindled cells with areas of haemorrhage and necrosis
IHC stain	CD31, CD34 Friend leukaemia virus integration	CD34, CD31, D2-40, ERG	CD31, D2-40, ERG (pleural fluid) CD31, M2A, ERG
RIAS treatment	Chemotherapy with gemcitabine and docetaxel	Chemotherapy with paclitaxel	Chemotherapy with paclitaxel
Prognosis	Disease progression- > death 4 months later	Disease progression- > death 4 months later	Ongoing chemotherapy (One out of 4 chemotherapy cycles)

Abbreviations: FDG, fludeoxyglucose; IHC, immunohistochemical; RIAS, radiation-induced angiosarcoma; RT, radiation therapy.

The radiation dose correlates with an increased risk.[6] Pleural involvement is exceedingly rare. In a SEER 18-registry database of 8 million cancer patients, 197 malignant radiation induced sarcoma were identified (0.0024)% and among these, only 3 patients had pleural involvement. Histology identified radiation induced fibrosarcoma,[1] spindle cell sarcoma[1] and synovial sarcoma.[1,5] Literature review has identified only two articles reporting RIAS involving the pleura.[7,8] These reports described patients presenting with pleural effusion, who had previously each received a total dose of 60 Gy radiotherapy to their lungs for primary malignancies of lung and gingiva squamous cell carcinoma respectively. Pleural biopsy in both cases showed proliferation of malignant tumour cells with positive immunohistochemical staining for CD31 and CD 34, confirming the diagnosis of RIAS. Despite chemotherapy treatment, both cases had disease

progression and death occurred approximately 4 months later (Table 1).

In addition to its rarity, the non-specific presentation of RIAS may further delay diagnosis. RIAS often presents with non-specific cutaneous manifestations such as eczematous rashes or purplish-red nodules within or around the previous radiation field,[1,2] posing additional diagnostic challenges. Although a biopsy of the rash was not performed in our case, histopathological examination can aid in the clinical diagnosis of RIAS. Histologically, RIAS typically shows large infiltrative vascular proliferations consisting of atypical endothelial cells with a high nuclear-cytoplasmic ratio, nuclear hyperchromasia, and irregular nuclear contours, involving the deep dermis and subcutaneous tissues. This helps differentiate RIAS from atypical vascular lesions or chronic radiation dermatitis.[2]

During diagnostic challenge, Cahan criteria, as modified by Arien et al. can be used to aid in the diagnosis of RIAS.[3,4] The average latency for a secondary sarcoma diagnosis post radiotherapy ranges between 8 and 14 years.[9] Careful histologic evaluation is then required for definitive diagnosis. Expression of at least one endothelial markers including factor VIII, FL-1, CD31, CD 34 can confirm the diagnosis of angiosarcoma, where CD34 is both most sensitive and specific.[10] Management is as for sarcomas of any histologic type with wide-margin surgical resection, albeit challenging due to anatomical location, fibrotic changes after irradiation, multifocal disease, or organ invasion. Chemotherapy and radiotherapy are options for metastatic disease, although the latter is less frequently used in previously irradiated patients due to potential toxicity, side effects and psychological barriers for treating patients with the same modality that caused the secondary malignancy.[11]

Despite intensive treatment, RIAS has a poor prognosis, with a 5-year disease-specific survival rate of 32%–58%.[12] With earlier detection of breast cancer and adjuvant radiotherapy following breast-conserving surgery becoming the standard treatment for early-stage breast cancer, the incidence of RIAS is expected to increase. Clinician and patient education on the clinical presentation of RIAS is important. Given the latency of RIAS, thorough clinical examination and surveillance imaging approximately 5 years after completion of radiotherapy are recommended for patients who have undergone radiotherapy.

AUTHOR CONTRIBUTIONS

The authors confirm contribution to the paper as follows: Author Jenny S. W. Yun patient data collection, consent collection, draft manuscript and preparations. Authors Vikas Wadhwa and James McCracken patient data interpretation and draft supervision. All authors reviewed the results and approved the final version of the manuscript.

CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

The authors declare that appropriate written informed consent was obtained for the publication of this manuscript and accompanying images.

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REFERENCES

1. Hui A, Henderson M, Speakman D, Skandarajah A. Angiosarcoma of the breast: a difficult surgical challenge. Breast. 2012;21(4):584–9.
2. Javed N, Stowman AM. Educational case: radiation-induced Angiosarcoma of the breast. Acad Pathol. 2021;8:23742895211060529.
3. Arlen M, Higinbotham NL, Huvos AG, Marcove RC, Miller T, Shah IC. Radiation-induced sarcoma of bone. Cancer. 1971;28(5):1087–99.
4. Cahan WG, Woodard HQ, Higinbotham NL, Stewart FW, Coley BL. Sarcoma arising in irradiated bone; report of 11 cases. Cancer. 1948;1(1):3–29.
5. Loap P, Kirova Y. Pleural radiation-induced sarcoma: a SEER population-based description of a rare entity. Rep Pract Oncol Radiother. 2021;26(2):318–9.
6. Sholl LM, Barletta JA, Hornick JL. Radiation-associated neoplasia: clinical, pathological and genomic correlates. Histopathology. 2017;70(1):70–80.
7. Miller R, Mudambi L, Vial MR, Kalhor N, Grosu HB. Radiation-induced Angiosarcoma as a cause of pleural effusion. Am J Respir Crit Care Med. 2017;196(4):e10–1.
8. Ogino H, Tobiume M, Kagawa K, Kawano H, Sakaguchi S, Saijo A, et al. Radiation-associated angiosarcoma presenting as massive pleural effusion. Intern Med. 2022;61(9):1393–7.
9. Callesen LB, Safwat A, Rose HK, Sørensen FB, Baad-Hansen T, Aggerholm-Pedersen N. Radiation-induced sarcoma: a retrospective population-based study over 34 years in a single institution. Clin Oncol (R Coll Radiol). 2021;33(5):e232–8.
10. Dainese E, Pozzi B, Milani M, Rossi G, Pezzotta MG, Vertemati G, et al. Primary pleural epithelioid angiosarcoma. A case report and review of the literature. Pathol Res Pract. 2010;206(6):415–9.
11. Spałek MJ, Czarnecka AM, Rutkowski P. The management of radiation-induced sarcomas: a cohort analysis from a sarcoma tertiary center. J Clin Med. 2021;10(4):694.
12. Snow A, Ring A, Struycken L, Mack W, Koç M, Lang JE. Incidence of radiation induced sarcoma attributable to radiotherapy in adults: a retrospective cohort study in the SEER cancer registries across 17 primary tumor sites. Cancer Epidemiol. 2021;70:101857.

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