Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.8195-21
Intern Med 61: 1393-1397, 2022
http://internmed.jp

【 CASE REPORT 】

Radiation-associated Angiosarcoma Presenting as Massive Pleural Effusion

Hirokazu Ogino[1], Makoto Tobiume[1], Kozo Kagawa[1], Hiroshi Kawano[1], Satoshi Sakaguchi[1], Atsuro Saijo[1], Daisuke Matsumoto[2], Hiromitsu Takizawa[2], Yuriko Morikawa[3], Yoshimi Bando[3], Hisatsugu Goto[1], Hiroshi Nokihara[1] and Yasuhiko Nishioka[1]

Abstract:
A 67-year-old man was admitted to our hospital for massive pleural effusion. He had a history of mandibular gingival carcinoma treated with radiation therapy (RT). Based on the cytology findings of pleural effusion and a thoracoscopic pleural biopsy, we finally diagnosed him with radiation-associated angiosarcoma. Retrospective cell-block immunocytochemistry with pleural effusion also showed potential utility for the diagnosis. This case highlights the importance of considering the possibility of radiation-associated secondary cancer in patients with pleural effusion who have a history of RT.

Key words: angiosarcoma, secondary cancer, radiation associated sarcoma, pleural effusion, thoracoscopic pleural biopsy, cell block immunocytochemistry

(Intern Med 61: 1393-1397, 2022)
(DOI: 10.2169/internalmedicine.8195-21)

Introduction

Improvements in the prognosis of patients with a variety of malignancies have resulted in the increased incidence of therapy-related complications, including secondary cancer (1). Radiation therapy (RT) is well-known to induce the development of several secondary malignant neoplasms, including soft tissue sarcoma (2). Radiation-associated sarcoma is defined as an iatrogenic disease related to prior radiation exposure, and the incidence has been estimated to be under 1% in adult patients receiving RT (3). The average duration between RT and the diagnosis of secondary sarcoma is reported to be 7 to 16 years (4-6), but it could happen as early as a few months to as long as 54 years later (7). Radiation-associated sarcoma accounts for 3-6% of all sarcomas (3), and the most common histological type is undifferentiated/unclassified soft tissue sarcoma, followed by angiosarcoma (8).

Angiosarcoma is a rare soft tissue sarcoma of endothelial cell origin with a poor prognosis (9). Most angiosarcomas arise spontaneously, involving the head and neck, and can be caused by RT or chronic lymphoedema. Therefore, especially among breast cancer patients treated with surgery and RT, the development of angiosarcoma has an impact on their prognosis (10). The initial presentations of angiosarcoma are typically cutaneous bruise or purplish-red papules and can be mistaken for benign lesions, resulting in a delayed diagnosis. Following the manifestation of pulmonary metastasis, the most common site of metastasis, it may present as a pleural disease or hemorrhagic pleural effusion (9).

We herein report a rare case of radiation-associated angiosarcoma after multimodality treatment for left mandibular gingival carcinoma showing massive pleural effusion and diagnosed by cell-block immunocytochemistry (ICC) as well as a thoracoscopic pleural biopsy.

Case Report

A 67-year-old man was admitted to our hospital with a

[1]Department of Respiratory Medicine and Rheumatology, Graduate School of Biomedical Sciences, Tokushima University, Japan, [2]Department of Thoracic, Endocrine Surgery and Oncology, Graduate School of Biomedical Sciences, Tokushima University, Japan and [3]Division of Pathology, Tokushima University Hospital, Japan
Received: June 21, 2021; Accepted: August 12, 2021; Advance Publication by J-STAGE: October 12, 2021
Correspondence to Dr. Yasuhiko Nishioka, yasuhiko@tokushima-u.ac.jp

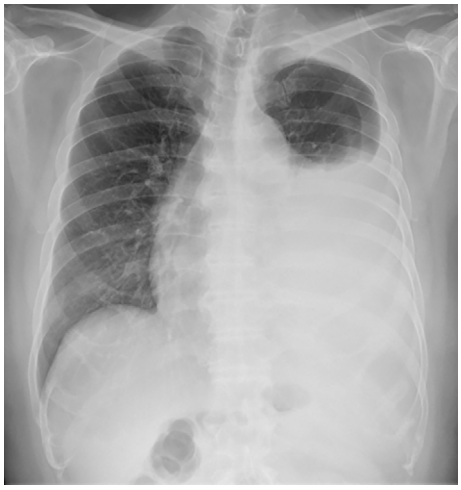

Figure 1. **Chest X-ray on admission. Massive pleural effusion was detected in his left lung field.**

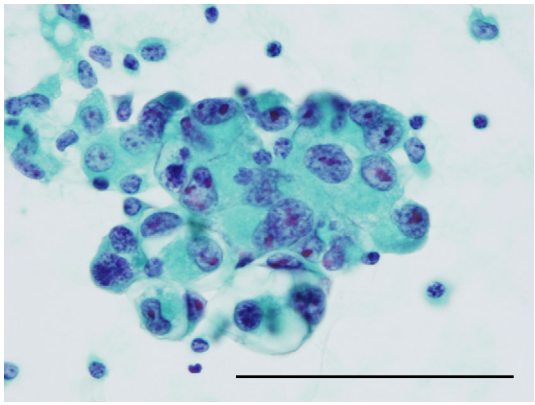

Figure 2. **Results of a cytology examination of the pleural effusion. Papanicolaou staining identified the aggregation of malignant cells showing eccentric nuclei and prominent nucleoli but not cornification. The bar indicates 100 μm.**

chief complaint of a fever and dyspnea. Regarding his medical history, he had had a left mandibular gingival squamous cell carcinoma eight years prior to this admission. He had received chemotherapy with S-1, intra-arterial chemotherapy with docetaxel, left mandibular resection with cervical lymph node dissection and reconstruction with a titanium plate, and RT (total 60 gray). RT was given to his left neck field and partially involved the mandible and lung apex. Furthermore, he had undergone surgery several times because of damage to or infection of the titanium plate. Thereafter, follow-up positron emission tomography-computed tomography (PET-CT) was performed every few years. He had smoked for 120 pack-years and had a history of exposure to asbestos.

Physical examinations showed rigidity and stiffness of the skin and soft tissue in his left neck field and the attenuation of his left breathing sounds. Chest X-ray showed massive left pleural effusion (Fig. 1). Laboratory data on admission showed elevated levels of inflammatory reaction markers, such as his white blood cell (WBC) count and C-reactive protein (CRP) level, but not of his tumor markers. On the day of admission, we inserted a chest tube and detected the drainage of bloody pleural effusion.

A cytology examination of the pleural effusion identified the aggregation of malignant cells showing eccentric nuclei and prominent nucleoli, but the cells did not show cornification (Fig. 2). Based on these findings, we suspected the malignant cells might be adenocarcinoma but not recurrence of mandibular gingival squamous cell carcinoma; however, we were unable to reach a definitive diagnosis.

Chest CT showed that the soft tissue in his left neck field was swollen (Fig. 3A) with thoracic wall thickening of the left apical portion (Fig. 3B), but no tumor shadow could be seen in the lung field. The most recent PET-CT scan, performed four months before admission, showed the abnormal uptake of ^{18}F-fluorodeoxyglucose (FDG) in the region (Fig. 3C, D), which was considered to be a postoperative reaction.

Severe rigidity and stiffness of the skin and soft tissue in his left neck field prevented us from performing a percutaneous biopsy, so we performed a thoracoscopic pleural biopsy. In the left thoracic cavity, we found the solid adhesion of the apical portion to the chest wall (Fig. 4A), pleural thickening (Fig. 4B), and pleural plaque (Fig. 4C) and performed a pleural biopsy of these regions and pleurodesis with talc.

In the pathological examinations, hematoxylin-eosin (H&E) staining of pleural tissues showed diffuse proliferation of malignant tumor cells with acidophilic cytoplasm and loose cell-cell adhesion (Fig. 5A). These findings were markedly different from the histology of the mandibular gingival squamous cell carcinoma tissue, which showed typical cancer pearls (Fig. 5B).

Immunohistochemistry (IHC) showed that the tumor cells were nearly all negative for pan-cytokeratin, p40, and mesothelioma markers, such as calretinin and WT-1, but strongly positive for vimentin (data not shown), suggesting the possibility of soft tissue sarcoma but not mesothelioma. Additional examinations revealed that the tumor cells were strongly positive for CD34, CD31, D2-40, and ERG (Fig. 5C and data not shown), resulting in the final diagnosis of radiation-associated angiosarcoma. We retrospectively performed cell-block ICC with his pleural effusion and obtained similar results (Fig. 5D, E).

We started chemotherapy with weekly paclitaxel (11) and observed a favorable anti-tumor effect temporarily. However, the tumor regrew after the seventh cycle of administration, and he ultimately died of tumor progression.

Discussion

Based on the clinical course, we considered several differential diagnoses of his carcinomatous pleurisy, including recurrence of mandibular gingival carcinoma in the thoracic cavity, malignant pleural mesothelioma, primary lung cancer, carcinoma of unknown primary, and secondary carcinoma.

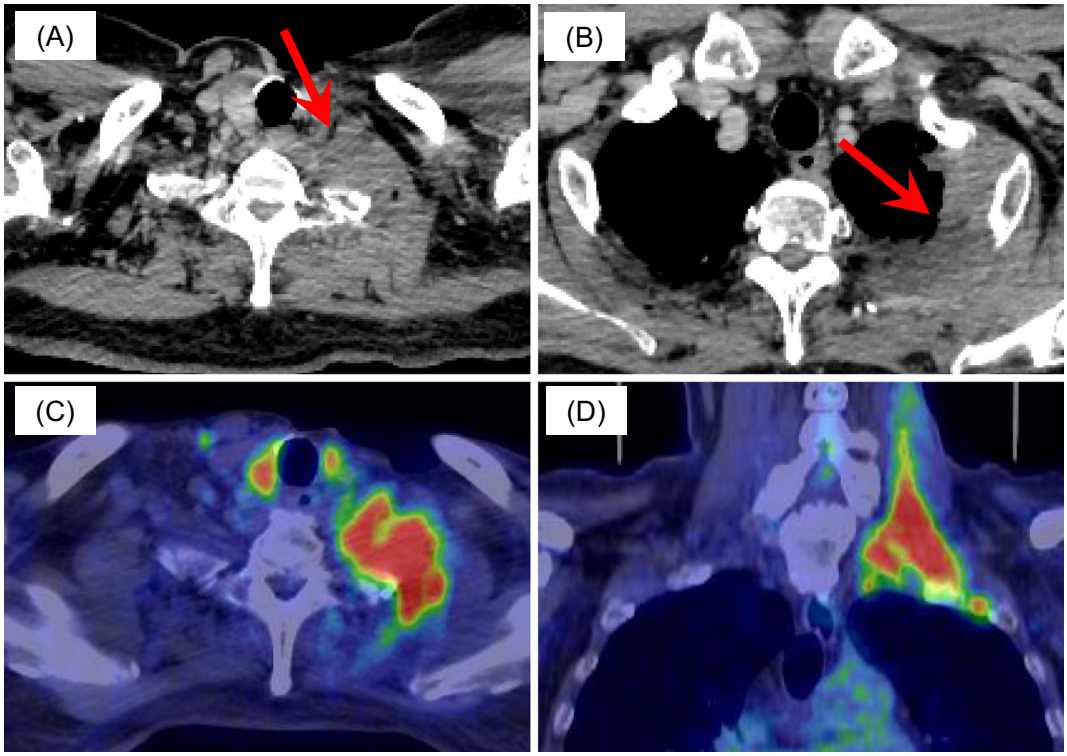

Figure 3. **Chest CT and PET-CT findings. Chest CT showed (A) the swollen soft tissue in his left neck field and (B) thoracic wall thickening of the left apical portion. (C, D) PET-CT performed four months before admission showed the abnormal uptake of ^{18}F-fluorodeoxyglucose (FDG) in his left neck field.**

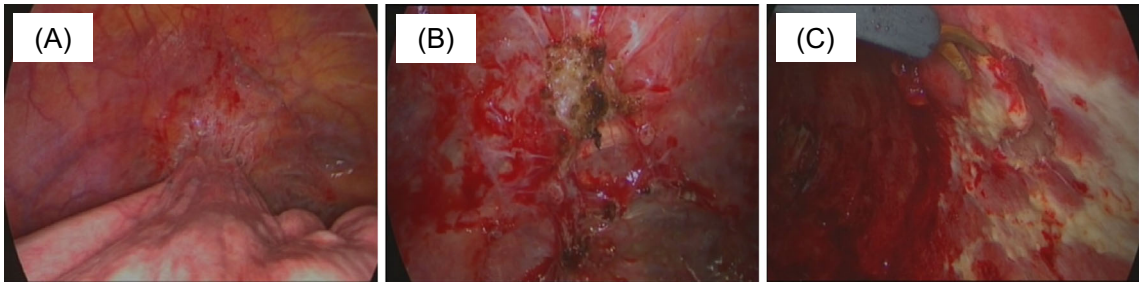

Figure 4. **Thoracoscopic findings. In the left thoracic cavity, (A) we found the solid adhesion of the apical portion to the chest wall, (B) pleural thickening after adhesiolysis, and (C) pleural plaques.**

The pleural tumors showed different morphological and IHC features from the previous oral carcinoma, denying the possibility of recurrence. Although this patient had a history of exposure to asbestos and pleural plaques, the IHC patterns were not consistent with malignant pleural mesothelioma. The vimentin expression indicated the possibility of a mesenchymal tumor, and the presence of CD34 expression, a typical marker of endothelial cells, ultimately resulted in the diagnosis of the pleural tumor as angiosarcoma. We therefore concluded that the angiosarcoma had been induced by RT in his left neck field and directly invaded the left thoracic cavity, resulting in the production of massive pleural effusion.

Only a few cases of angiosarcoma with the onset of pleural effusion have previously been reported (12-14); however, the angiosarcoma cells, primarily arose in pleura or hematogenously metastasized to the lung and thereafter produced the pleural effusion observed in these patients. To our knowledge, this is the first reported case of radiation-associated angiosarcoma in the neck field showing massive pleural effusion due to direct invasion to the thoracic cavity.

In addition to this case, the utility of a thoracoscopic pleural biopsy has been reported for the diagnosis of carcinomatous pleurisy induced by angiosarcoma (13-15). Along with thoracoscopy, an alternative diagnostic approach needs to be established for patients who are unable to undergo surgery, such as elderly patients. Cell-block ICC is considered useful for diagnosing malignant pleural effusion, especially for patients in whom a conventional cytology examination does not result in a definitive diagnosis (15), and is widely used in clinics for patients suspected of having mesothelioma or lung cancer. One report previously showed the util-

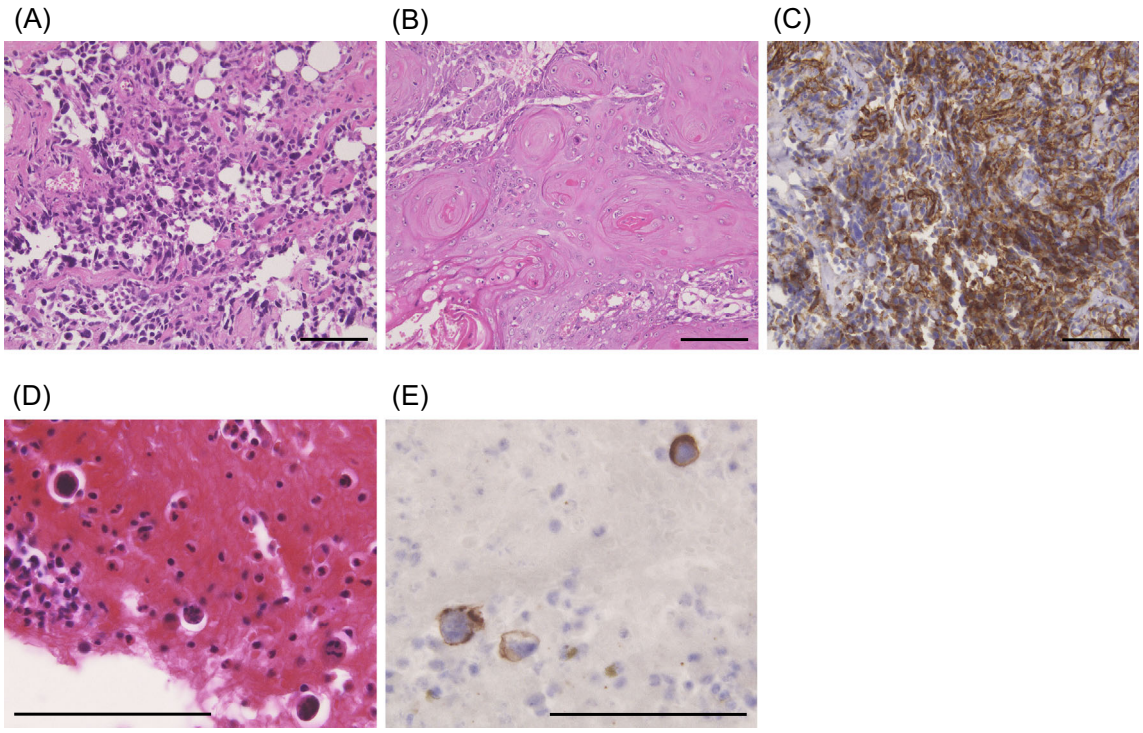

Figure 5. The histological findings. (A) Hematoxylin and Eosin (H&E) staining of pleural tissues showed diffuse proliferation of malignant tumor cells with acidophilic cytoplasm and loose cell-cell adhesion. (B) The previous mandibular gingival carcinoma tissue showed well-differentiated squamous carcinoma with typical cancer pearls. (C) The tumor cells of the pleural tissue strongly expressed CD34. (D, E) H&E staining and CD34 staining of the tumor cells using a cell block from pleural effusion. The cell block was made when the tumor relapsed after the initial chemotherapy. Enlarged tumor cells were detected in the bloody background, and the tumor cells were positive for CD34. The bar indicates 100 μm.

ity of cell-block ICC to diagnose the malignant pleural effusion caused by angiosarcoma (16), and other reports showed that ICC with fine-needle aspiration specimens resulted in a definitive diagnosis of angiosarcoma (17-19). In the present case, we retrospectively performed cell-block ICC and obtained consistent results (Fig. 5E), indicating that cell-block ICC has potential utility for diagnosing angiosarcoma and should be performed proactively.

Recently, anti-angiogenic regents, such as pazopanib, a small-molecule compound that inhibits multiple tyrosine kinases, including vascular endothelial growth factor receptor 2 (VEGFR-2), and bevacizumab, a monoclonal antibody for VEGF, showed partial clinical benefit for angiosarcoma (20-22). Although we were unable to treat this patient with pazopanib because of the bleeding tendency, these agents are expected to improve the prognosis of angiosarcoma, especially for patients with pleural effusion.

Conclusion

In summary, we experienced a rare case of radiation-associated angiosarcoma that developed with massive pleural effusion. It arose in his neck field after multimodality therapies against mandibular gingival carcinoma and directly invaded the thoracic cavity. Cell block ICC as well as a thoracoscopic pleural biopsy are considered useful for making such a diagnosis. This case highlights the importance of considering the possibility of radiation-associated secondary cancer in cases with a history of RT.

The authors state that they have no Conflict of Interest (COI).

References

1. Huvos AG, Woodard HQ, Cahan WG, et al. Postradiation osteogenic sarcoma of bone and soft tissues. A clinicopathologic study of 66 patients. Cancer **55**: 1244-1255, 1985.
2. Maddams J, Parkin DM, Darby SC. The cancer burden in the United Kingdom in 2007 due to radiotherapy. Int J Cancer **129**: 2885-2893, 2011.
3. Mark RJ, Bailet JW, Poen J, et al. Postirradiation sarcoma of the head and neck. Cancer **72**: 887-893, 1993.
4. Riad S, Biau D, Holt GE, et al. The clinical and functional outcome for patients with radiation-induced soft tissue sarcoma. Cancer **118**: 2682-2692, 2012.
5. Lagrange JL, Ramaioli A, Chateau MC, et al. Sarcoma after radiation therapy: retrospective multiinstitutional study of 80 histologically confirmed cases. Radiation Therapist and Pathologist Groups of the Fédération Nationale des Centres de Lutte Contre le Cancer. Radiology **216**: 197-205, 2000.
6. Mavrogenis AF, Pala E, Guerra G, Ruggieri P. Post-radiation sarcomas. Clinical outcome of 52 Patients. J Surg Oncol **105**: 570-576, 2012.
7. De Smet S, Vandermeeren L, Christiaens MR, et al. Radiation-

induced sarcoma: analysis of 46 cases. Acta Chir Belg **108**: 574-579, 2008.

8. Cha C, Antonescu CR, Quan ML, Maru S, Brennan MF. Long-term results with resection of radiation-induced soft tissue sarcomas. Ann Surg **239**: 903-909; discussion 909-910, 2004.

9. Young RJ, Brown NJ, Reed MW, Hughes D, Woll PJ. Angiosarcoma. Lancet Oncol **11**: 983-991, 2010.

10. Torres KE, Ravi V, Kin K, et al. Long-term outcomes in patients with radiation-associated angiosarcomas of the breast following surgery and radiotherapy for breast cancer. Ann Surg Oncol **20**: 1267-1274, 2013.

11. Penel N, Bui BN, Bay JO, et al. Phase II trial of weekly paclitaxel for unresectable angiosarcoma: the ANGIOTAX Study. J Clin Oncol **26**: 5269-5274, 2008.

12. 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 **196**: e10-e11, 2017.

13. Durani U, Gallo de Moraes A, Beachey J, Nelson D, Robinson S, Anavekar NS. Epithelioid angiosarcoma: a rare cause of pericarditis and pleural effusion. Respir Med Case Rep **24**: 77-80, 2018.

14. Moriya Y, Sugawara T, Arai M, et al. Bilateral massive bloody pleurisy complicated by angiosarcoma. Intern Med **46**: 125-128, 2007.

15. Fetsch PA, Abati A. Immunocytochemistry in effusion cytology: a contemporary review. Cancer **93**: 293-308, 2001.

16. Amano Y, Obana Y, Nakanishi Y, et al. [A case of angiosarcoma of the scalp with invasion to the pleural effusion - Diagnosis by cytology with immunohistological examination]. J Nihon Univ Med Ass **74**: 113-116, 2015 (Abstract in English).

17. Boucher LD, Swanson PE, Stanley MW, Silverman JF, Raab SS, Geisinger KR. Cytology of angiosarcoma. Findings in fourteen fine-needle aspiration biopsy specimens and one pleural fluid specimen. Am J Clin Pathol **114**: 210-219, 2000.

18. Sharma S, Singh P, Gupta P, Lal A, Srinivasan R. Primary splenic angiosarcoma with liver metastasis: a rare neoplasm diagnosed on fine-needle aspiration cytology and cell block immunocytochemistry. J Cytol **35**: 114-116, 2018.

19. Jung MJ, Kim YO. A case of metastatic angiosarcoma diagnosed by liquid-based preparation: peculiar cytoplasmic changes. Korean J Pathol **48**: 241-247, 2014.

20. Kollár A, Jones RL, Stacchiotti S, et al. Pazopanib in advanced vascular sarcomas: an EORTC Soft Tissue and Bone Sarcoma Group (STBSG) retrospective analysis. Acta Oncol **56**: 88-92, 2017.

21. Agulnik M, Yarber JL, Okuno SH, von Mehren M, et al. An open-label, multicenter, phase II study of bevacizumab for the treatment of angiosarcoma and epithelioid hemangioendotheliomas. Ann Oncol **24**: 257-263, 2013.

22. van der Graaf WT, Blay JY, Chawla SP, et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet **379**: 1879-1886, 2012.