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Case Report

Microsatellite-Stable Radiation-Induced Angiosarcoma after Breast-Conserving Surgery: A Case Report

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Keywords
Radiation-induced angiosarcoma · Breast cancer · Surgery · Microsatellite instability

Abstract
Radiation-induced angiosarcoma (RIAS) after breast-conserving surgery is quite rare. Risk factors for RIAS have yet to be identified, due largely to the very low incidence of this disease. The etiologic mechanisms of RIAS are not understood, although some reports suggest that genome instability may contribute to RIAS development. An 81-year-old Japanese woman presented to our hospital after developing multiple dark purple nodules on her left breast. She had undergone breast-conserving surgery for left breast cancer and adjuvant radiotherapy for the conserved breast 9 years earlier. Punch biopsy of one of the dark purple nodules was performed and the pathological diagnosis was angiosarcoma. She underwent total mastectomy with an adequate margin, and skin collected from her left thigh was grafted onto the site. Pathologically, the surgical margin was negative. The tumor was negative for microsatellite instability (MSI). Considering her age, she has remained under careful observation with neither systemic treatment nor adjuvant radiation. The only standard therapy for RIAS currently available is complete resection. Hence, early detection is crucial to obtain an adequate margin, followed by careful observation after breast-conserving surgery. It is also essential to reveal the tumor etiology, and for that purpose, we believe that the MSI status may be beneficial for the further investigation of RIAS.

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Introduction

Angiosarcoma of the breast is quite rare, accounting for only 0.04% of malignant breast tumors [1], and can be divided into primary and secondary types. There are several causes of secondary angiosarcoma of the breast: chronic lymphedema after total mastectomy with axillary dissection (Stewart-Treves syndrome) [2] and radiotherapy after breast-conserving surgery. The frequency of radiation-induced angiosarcoma (RIAS) is considered to be in the approximate range of 0.14–0.5% among patients who had breast-conserving surgery with radiotherapy [3, 4]. Risk factors for RIAS have yet to be identified, due largely to the very low incidence of this disease. Secondary angiosarcoma usually presents with various symptoms such as erythema, purpura, ulcers, and edema. Due to the broad range of possible symptoms, it is frequently misdiagnosed as skin changes caused by injury, infections, lymphedema, and X-ray dermatitis [5].

The current therapy for RIAS is mastectomy to achieve complete excision of the tumor with an adequate margin. Evidence-based standard systemic treatment has yet to be established for this rare disease, although a case report noted the effects of weekly paclitaxel for RIAS [6]. Radiotherapy for RIAS is controversial because there is concern that re-irradiating skin that has already been subjected to irradiation may result in local recurrence. The outcomes of patients with RIAS of the breast are poor. The 5-year survival rates reported in the literature range from 28 to 54% [4, 7]. The most common sites of distant metastasis are the contralateral breast, lymph nodes, lungs, pleura, bones, liver, and distant skin [3]. Nevertheless, overall survival was significantly prolonged in patients presenting with resectable disease (2-year overall survival 71.1, vs. 33.3% for those with nonresectable disease, $p < 0.001$). Thus, early detection of RIAS is essential for improving the outcomes of patients undergoing complete resection [8].

Case Presentation

An 81-year-old Japanese woman presented to our hospital with dark purple nodules with erythema on her left breast (Fig. 1). She had a history of left breast cancer and had undergone breast-conserving surgery 9 years previously at our institution. Histologically, her breast cancer was secretory carcinoma and was classified as pT2N0M0 pStage IIA. Her tumor was immunohistochemically estrogen receptor positive, progesterone receptor negative, and HER2 negative.

Adjuvant radiotherapy (50 Gy/25 fractions) was performed for the conserved breast, followed by chemotherapy (FEC, 4 cycles) and endocrine therapy (anastrozole, 1 mg daily for 5 years). She also had a history of pancreatic cysts and had undergone laparoscopic caudal

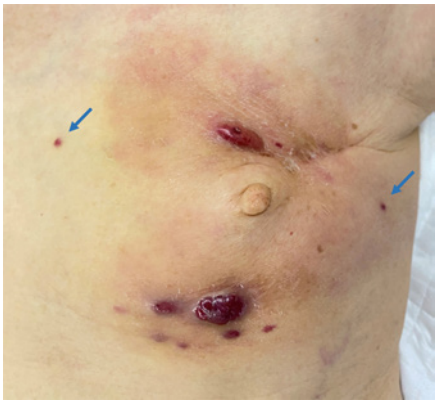

Fig. 1. Clinical photograph. Multiple dark purple nodules surrounding erythema of the left breast were noted at the first physical examination. The innermost and outermost nodules were also thought to be lesions (blue arrows).

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pancreatectomy 2 years prior to the diagnosis of RIAS. Her pancreatic cysts were serous cystadenoma histologically. Her family history included her mother and sister having had gastric and pancreatic cancers, respectively. However, no one had a history of breast or ovarian cancer. Ultrasound revealed 2 superficial masses in her left breast, which were irregular in shape. These masses were hypoechoic and measured 17 mm in diameter in the upper area and 10 mm in the lower area, suggesting skin involvement (Fig. 2). Doppler signaling indicated that both tumors were hypervascular. Punch biopsy was performed for one of the dark purple nodules and the pathological diagnosis was angiosarcoma. MRI (magnetic resonance imaging) revealed 4 irregular masses with heterogeneous enhancement (Fig. 3). On a positron

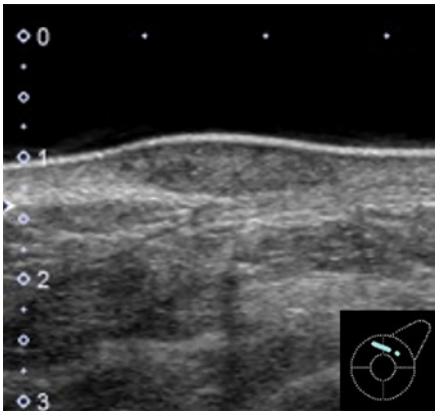

Fig. 2. Findings on ultrasound. Ultrasound revealed an irregularly shaped mass which suggested skin involvement.

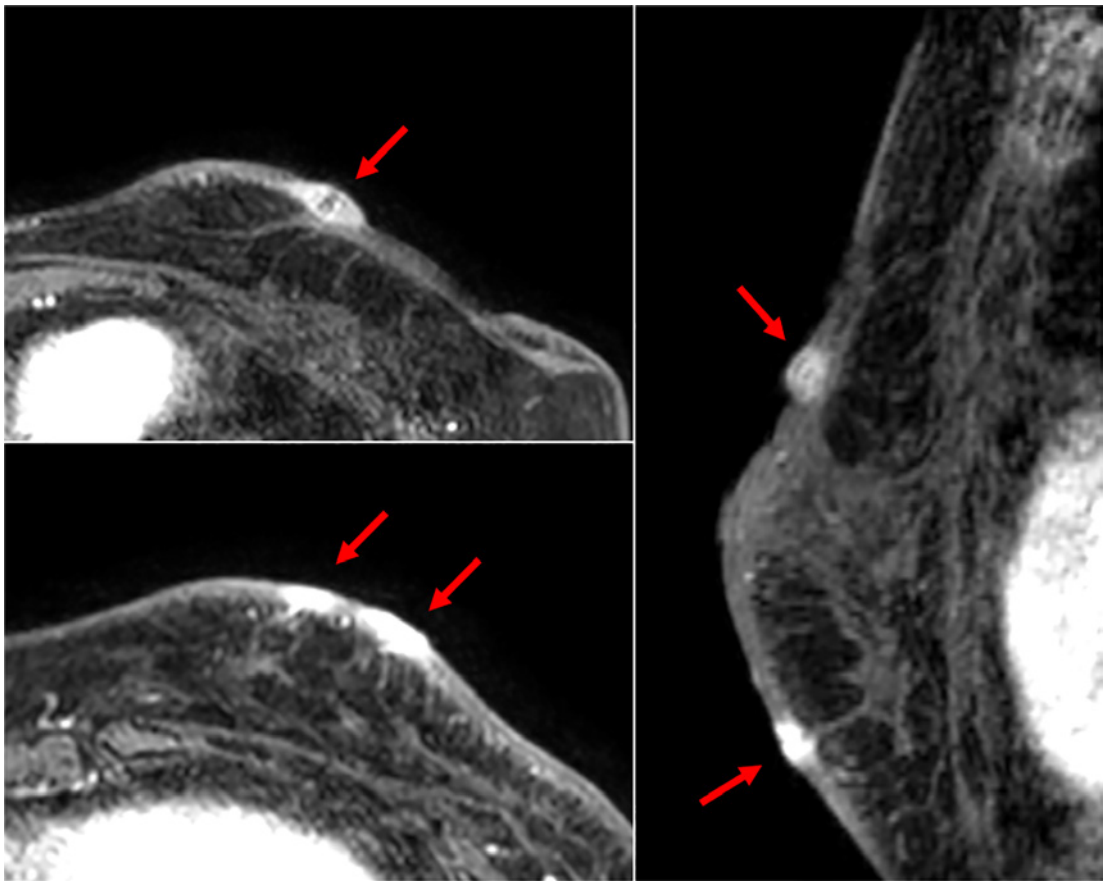

Fig. 3. MRI findings. MRI revealed multiple irregular masses with heterogeneous enhancement (red arrows).

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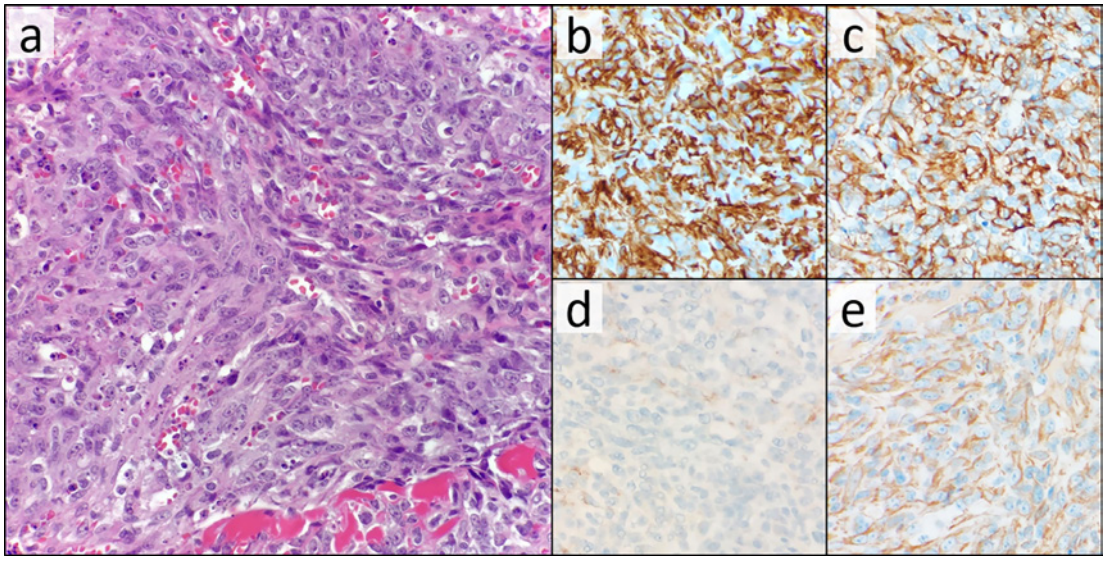

Fig. 4. Histopathologic findings from the surgical specimen. **a** Atypical endothelial cells, creating irregular vessels in subcutaneous tissue, were demonstrated by staining (hematoxylin and eosin). **b–e** Immunohistochemical findings for CD31 (**b**), CD34 (**c**), von Willebrand factor (**d**), and vimentin (**e**).

emission tomography-computed tomography scan, high fluorodeoxyglucose uptake (SUV_{max} 7.83) in the left breast was observed, but there were no hotspots in other organs.

Based on the imaging findings, we judged her disease to be resectable and performed total mastectomy with a wide skin resection (1 cm from the edge of the tumor and the skin discoloration). After we had confirmed all surgical margins to be negative intraoperatively, skin collected from her left thigh was grafted onto the site.

Pathologically, there were multiple lesions, with a maximum size of 13 mm, but none were continuous. Atypical endothelial cells, creating irregular vessels in subcutaneous tissue, were confirmed (Fig. 4a). On immunohistochemical staining, the tumor cells were positive for markers of angiosarcoma such as CD31, CD34, von Willebrand factor (focally), and vimentin (Fig. 4b–e). The surgical margin was negative. We also investigated microsatellite instability (MSI), following the approval of MSI determination as a companion diagnostic test in Japan. The MSI testing was outsourced to SRL Inc. (Tokyo, Japan). Using a kit by FALCO, the MSI status was examined and judged to be microsatellite stable; all markers (BAT-25, BAT-26, NR-32, NR-24, and MONO-27) were negative. Considering her advanced age, the patient has remained under careful observation without systemic treatment and/or adjuvant radiation and has been free of recurrence for 6 months to date.

Discussion and Conclusion

BRCA1/2 mutation carriers are reportedly at high risk of developing RIAS [9]. Double-stranded DNA damage induced by radiation, which results in genome instability, is considered to contribute to RIAS development. This is why we investigated the MSI status in the current case. However, our case was MSI negative. To the best of our knowledge, this is the first report to determine the MSI status of a patient with RIAS, although the MSI testing yielded negative results. We presume that the MSI status as well as accumulation of data from more RIAS cases would be beneficial for understanding the disease etiology.

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RIAS usually occurs in elderly women and develops long after radiotherapy administered postoperatively for breast cancer, as previously reported [8]. The mean age at onset and time after radiotherapy were 72 years (range 51–93) and 7.5 years (range 1–26), respectively, according to these earlier reports from Western countries. For comparison, we investigated RIAS case reports from Japan published since 2011 [10–15]. The mean age of the 8 patients, including our case, was 73 years, and the mean duration from radiotherapy to RIAS onset was 7 years, similar to the values reported from Western countries.

RIAS is also known to frequently develop as multifocal lesions [4]. Multifocality was seen in 3 of 8 (37.5%) recent case reports from Japan, including our case. The reasons for the long period of time elapsed between radiotherapy and the appearance of such multifocal lesions are unknown. Interestingly, Tanaka et al. [11] reported a RIAS case showing spontaneous regression after fine-needle aspiration biopsy. They suggested that an immune response triggered by the biopsy had induced spontaneous regression of the disease. Our patient had undergone surgery for pancreatic serous cystadenoma under general anesthesia 2 years prior to the current presentation. This raised the possibility that the invasive event of pancreatic surgery had weakened her immune system, triggering the onset of RIAS. Of the aforementioned Japanese cases, the medical history was unfortunately unknown for the majority of them. Only 1 patient, whose medical history was available, underwent surgery under general anesthesia for some reasons. She had received partial resection of a contralateral breast cancer, clipping of a brain aneurysm, cholecystectomy for cholelithiasis 6 years before RIAS, and distal gastrectomy for gastric cancer 5 years before [11]. In hopes of elucidating the oncogenic mechanism underlying RIAS development, we advocate accumulating detailed medical histories for these patients.

The only standard therapy currently available for RIAS is complete resection. Hence, early detection is crucial to obtaining an adequate surgical margin. We must carefully observe patients, considering that this disease tends to develop late and to present with a broad range of symptoms, which can be difficult to differentiate from skin diseases. In our view, MSI status, which may contribute to understanding the etiology of RIAS, might be worth investigating in more RIAS cases.

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Statement of Ethics

Written informed consent for the publication of the present case report and any accompanying images was obtained from the patient.

Conflict of Interest Statement

The authors declare that they have no conflicts of interest to disclose.

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Author Contributions

Y.I. contributed to writing of the manuscript. Y.H. was involved in drafting the manuscript. Y.H., H.O., and A.A. conducted the histological assessment. Y.I. and M.S. were responsible for overall care of the patient. M.S. reviewed and edited the manuscript. All authors contributed to discussions and agreed on the final version of the submitted manuscript.

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