PD-L1-Expressing Radiation-Associated Angiosarcoma after Primary Breast Cancer

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Abstract
Radiation-associated angiosarcoma (RAAS) is a type of radiation-associated sarcoma (RAS) that develops at the previous field of radiation in breast cancer patients. Although several reports have suggested a poor prognosis for RAAS, the 5-year overall survival of RAAS is better than that of cutaneous angiosarcoma (CAS), suggesting that the prognostic factors of RAAS and CAS might be different, at least in part. In this report, we describe a case of RAAS, and employed immunohistochemical (IHC) staining of PD-L1 and MMP9 as well as perios tin, IL-4, and CD163. Interestingly, IHC staining revealed that the RAAS in our case was positive for PD-L1 and negative for MMP9. Moreover, the predominant stromal factor of our case was perios tin, suggesting that TAMs in the present case was not immunosuppressive, but an inflammatory subtype. These results might explain, at least in part, the better prognosis of RAAS compared to CAS.
Introduction

Radiation-associated angiosarcoma (RAAS) is a type of radiation-associated sarcoma (RAS) that develops at the previous field of radiation in breast cancer patients [1–3]. RAAS is reported as the most common RAS in the breast region, which rarely occurs but is increasing in number because of the improved prognosis of breast cancer [1, 2]. Although several reports have suggested a poor prognosis for RAAS [1–3], the 5-year overall survival of RAAS is better than that of cutaneous angiosarcoma (CAS) [1, 4], suggesting that the prognostic factors of RAAS and CAS might be different, at least in part. In this report, we describe a case of PD-L1 expressing RAAS, and discuss possible prognostic factors for RAAS.

Case Report

A 79-year-old Japanese woman visited our outpatient clinic with asymptomatic red nodules with pruritic erythema. She had undergone a right breast partial mastectomy followed by adjuvant chemoradiotherapy (docetaxel, cyclophosphamide with 40 Gy/20 Fr) for the treatment of invasive ductal carcinoma in another institute 5 years previously. On her initial visit, physical examination revealed multiple red nodules with purpuric erythema on the irradiated lesions (Fig. 1a). A biopsy specimen from a red nodule revealed a dense infiltration of band-like spindle cells with irregularly anastomosing vascular channels lined by single layers of enlarged endothelial cells (Fig. 1b). Immunohistochemical (IHC) staining revealed that these atypical cells were positive for CD31 (Fig. 1c) and CD34 (Fig. 1d). From the above findings, our diagnosis was RAAS. Since RAAS had developed at previously irradiated site, we excised the tumor with a 20-mm margin. In addition, we administered paclitaxel at 80 mg/m² on days 1, 8, and 15 of a 4-week cycle.

To further investigate the possible immunological background of RAAS, we employed IHC staining for periostin (Fig. 2a), IL-4 (Fig. 2b), CD163 (Fig. 2c), PD-L1 (Fig. 3a), and MMP9 (Fig. 3b). IHC staining revealed that the atypical spindle cells and stromal histiocytes expressed PD-L1. In contrast, MMP9 was slightly expressed both on tumor cells and stromal cells. CD163+ tumor-associated macrophages (TAMs), which are abundant with periostin, were densely infiltrated at the tumor sites.

Discussion

RAAS of the breast is a rare, aggressive disease that develops at the radiation site of breast cancer patients [1]. Although the prognosis of RAAS is poor, a systematic review reported by Depla et al. [1] suggested that the 5-year overall survival of RAAS is 43%, which is better than that of CAS (31–35%) [4]. These reports suggested that the prognostic factors for RAAS and CAS might be different. Since previous reports suggested that two of the prognostic factors for RAAS are tumor size and age [1], both of which are also major prognostic factors for CAS [5], and other prognostic factors might be responsible for the better prognosis of RAAS compared to CAS. For example, Honda et al. [6] reported that PD-L1 expression is a better prognostic marker of CAS. In addition, approximately 80% of CAS expresses matrix metalloproteinase (MMP9) [7], which is also reported to be a poor prognostic factor for various skin cancers [8, 9]. These reports suggest that PD-L1 and MMP9 might represent different prognostic factors between RAAS and CAS.
TAMs, which compose an immunosuppressive microenvironment and are widely detected in skin cancers including CAS [10, 11], might be another prognostic factor for RAAS. Indeed, previous reports have suggested that PD-L1 expression in TAMs is necessary for antigen-specific tolerance induction in tumor-bearing hosts [10, 12]. TAMs produce angiogenetic factors such as VEGF and MMPs to induce neovascularization in sarcoma [10, 13]. Since TAMs are characterized by their heterogeneity and plasticity that can be functionally reprogrammed to polarized phenotypes by exposure to stromal factors [8], it is important to evaluate stromal factor to predict the function of TAMs.

From the above findings, we employed IHC staining for PD-L1 and MMP9, as well as periostin, IL-4, and CD163. IHC staining revealed that the RAAS in our case was positive for PD-L1 and negative for MMP9. Moreover, the predominant stromal factor of our case was periostin, suggesting that the TAMs in our present case were not immunosuppressive, but inflammatory subtypes [14]. These results might explain, at least in part, the better prognosis of RAAS compared to CAS. Since we present only a single case, further cases are needed to gain additional insight into the pathomechanisms of RAAS.

Statement of Ethics

The patient gave written informed consent.

Disclosure Statement

The authors have no conflicting interests to declare.

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Fig. 1. a Multiple red nodules with purpuric erythema on the irradiated lesions. b A dense infiltration of a band-like spindle cells with irregularly anastomosing vascular channels lined by single layers of enlarged endothelial cells. H&E staining. Paraffin-embedded tissue samples from the right shoulder were deparaffinized and stained with anti-CD31 Ab (c) and anti-CD34 Ab (d). Original magnification, ×100 (b–d).
Fig. 2. Paraffin-embedded tissue samples from the right shoulder were deparaffinized and stained with anti-periostin Ab (a), anti-IL-4 Ab (b), and anti-CD163 Ab (c). Original magnification, ×200 (a), ×100 (b, c).
Fig. 3. Paraffin-embedded tissue samples from the right shoulder were deparaffinized and stained with anti-PD-L1 Ab (a) and anti-MMP9 Ab (b). Original magnification, ×200 (a, b).