SHORT COMMUNICATION

Radiotherapy-induced Angiosarcoma Mimicking Merkel Cell Carcinoma Metastases

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Cutaneous angiosarcoma is a rare and highly aggressive tumour. It constitutes 1–2% of all sarcomas, which themselves account for about 1% of all malignancies. Even more rare is the subtype of secondary radiotherapy-induced angiosarcoma (RIAS), which can develop several years following radiation therapy, most frequently arising on the chest after breast cancer treatment with an average latency period of 4–8 years (1–4). To the best of our knowledge, no cases have been reported following radiotherapy of Merkel cell carcinoma. Diagnosis is based on clinical suspicion and histopathological confirmation. Clinically, angiosarcoma often presents initially as a nonspecific erythema, with the development of nodules and bleeding at a later stage. Histopathologically, these sarcomas show a dissecting network of deep-reaching non-functional vascular channels, sometimes with only minimal endothelial atypia. In contrast to benign haemangiomas, angiosarcomas stain positive for podoplanin (1).

RIAS is a cancer with a very poor prognosis due to its high recurrence rate and risk of distant metastasis. In breast cancer, the benefits of local radiotherapy significantly outweigh the risk of developing angiosarcoma (4).

The primary treatment for radiotherapy-induced angiosarcoma is wide surgical resection. Reports on reirradiation in previously irradiated fields are limited, and its benefit – mainly reduced local recurrence without a survival advantage – must be balanced against the risks of retreatment (1). Even though some data suggest a benefit of doxorubicin and ifosfamide-based adjuvant chemotherapy in adult soft tissue sarcomas (1, 5–7), there are no studies on its benefit for RIAS (8).

Merkel cell carcinoma is a rare, aggressive primary skin malignancy with both epithelial and neuroendocrine differentiation. Clinically, it manifests as a rapidly enlarging, reddish, spherical nodule with a smooth, shiny surface and firm-elastic consistency (9). Spontaneous regressions are observed, likely due to immune mechanisms, leading to favourable responses to immunomodulating therapies. Management typically involves excision, sentinel lymph node biopsy, and evaluation by a tumour board for treatment decisions (9).

CASE REPORT

A 78-year-old male with a history of lymphatically metastasized Merkel cell carcinoma on his left upper arm presented to our dermatological outpatient clinic with rapidly developing erythematous nodules on the left chest (**Fig. 1**). He reported that the lesions had increased in size over a few days but denied any significant discomfort or B symptoms (fever, night sweats, weight loss). For the treatment of the Merkel cell carcinoma, he had undergone guideline-conform resection with a 2 cm safety margin, left axillary dissection, and postoperative radiation therapy 6 years earlier. Follow-up examinations had always been unremarkable until the current presentation. He stated that he had called his dermatologist to report the new skin lesions and that the latter had reassured him with the recommendation to show them to him at his next scheduled follow-up appointment after 2 months. As he did not want to wait that long, he presented to our clinic.

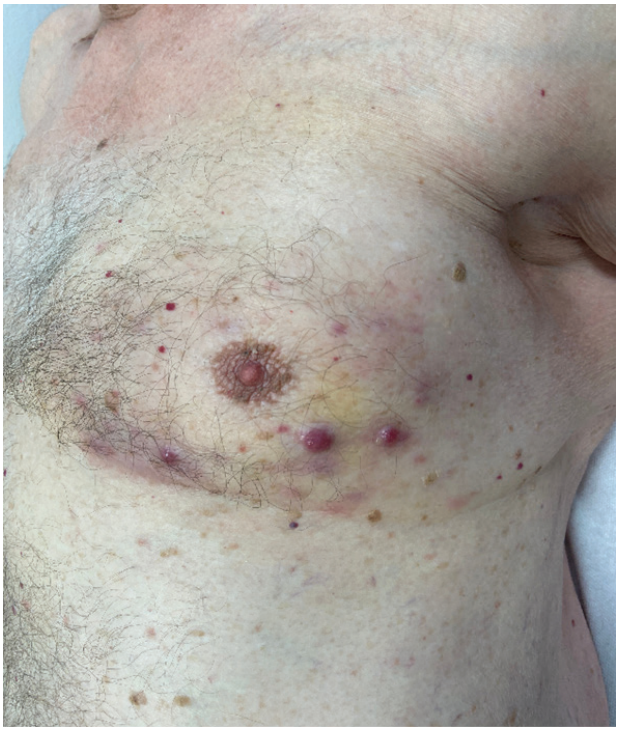

Fig. 1. Clinical presentation observed during initial assessment in our clinic.

Upon examination, the patient exhibited several well-demarcated, shiny, erythematous, firm nodules with a diameter of 5–8 mm on the left pectoral side. The left chest was notably enlarged compared with the right but was not tender upon palpation. Lymph node palpation did not reveal any abnormal findings and there was no evidence of local recurrence in the area of the primary scar or in transit metastases. The rest of the skin examination was unremarkable as well.

Given the immediate suspicion of secondary metastasis from the Merkel cell carcinoma, a biopsy of the nodules was performed. An initial haematoxylin and eosin (H&E) staining revealed a dense malignant infiltrate in the dermis (**Fig. 2**) that morphologically resembled a skin metastasis of Merkel cell carcinoma. However, immunohistochemically, the tumour cells were negative for the Merkel cell carcinoma marker Cytokeratin 20 (CK20), and likewise for the melanoma markers S100 and SOX-10, but strongly

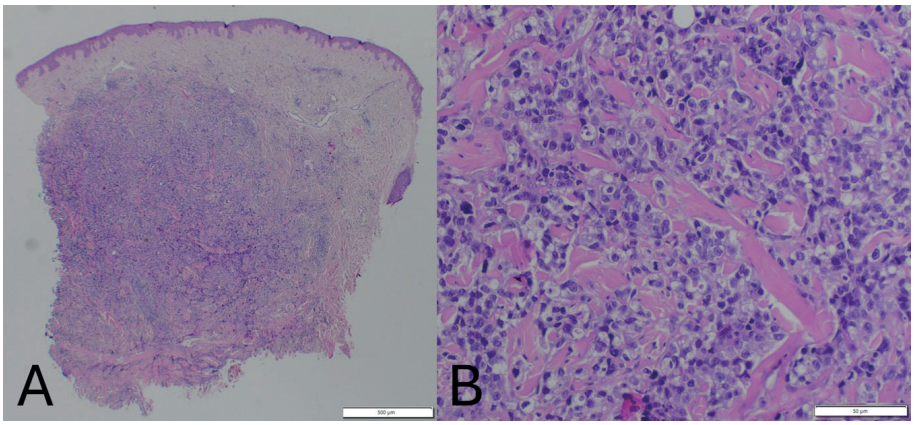

Fig. 2. Histopathological examination revealed a dense, unencapsulated, and poorly circumscribed dermal proliferation composed of atypical epithelioid cells with enlarged, hyperchromatic nuclei forming solid nests and irregular, anastomosing vascular channels, with several atypical mitotic figures. Haematoxylin and eosin (H&E) stain; original magnifications (A) 50x, bar=500 μm, and (B) 200x, bar=50 μm.

positive for D2-40, CD31, and ERG, with a 60% positivity for Ki-67 (MiB1), and negativity for smooth muscle actin (SMA). This profile was consistent with angiosarcoma. Additionally, approximately 50% of the tumour cells expressed c-Myc, which is a characteristic marker for radiation-induced angiosarcoma (RIAS) (**Fig. 3**).

Subsequent imaging with MRI revealed a cutaneous and subcutaneous, partially nodular, diffuse thickening of the left chest, consistent with the histologically confirmed angiosarcoma. The margins of the angiosarcoma were not clearly delineated on MRI. Staging with PET/CT scan did not reveal any distant metastases. The case was discussed in our multidisciplinary tumour board for bone and soft tissue sarcomas, and surgical resection was recommended.

The patient underwent extensive excision of the tumour while preserving the pectoralis minor and serratus anterior muscles, including all associated soft tissues. The fascia of the intercostal muscles was preserved. The resulting defect was reconstructed using a latissimus dorsi flap undertaken by the plastic surgery team.

DISCUSSION

In clinical practice, it is crucial to remain vigilant for rare entities, as common conditions frequently dominate the diagnostic landscape, often obscuring atypical presentations (colloquially referred to as "zebras"). In our case, we successfully identified a significant and rare entity by immunohistochemistry. Here, the diagnostic clue was the expression of c-Myc, which has been identified as a recurrent genetic alteration in secondary angiosarcomas induced by radiotherapy, but not in primary angiosarcomas or atypical vascular lesions following radiation (10). Thus, this staining together with the vascular marker podoplanin proved crucial in establishing the correct diagnosis.

This case highlights the critical importance of comprehensive histological and immunohistochemical

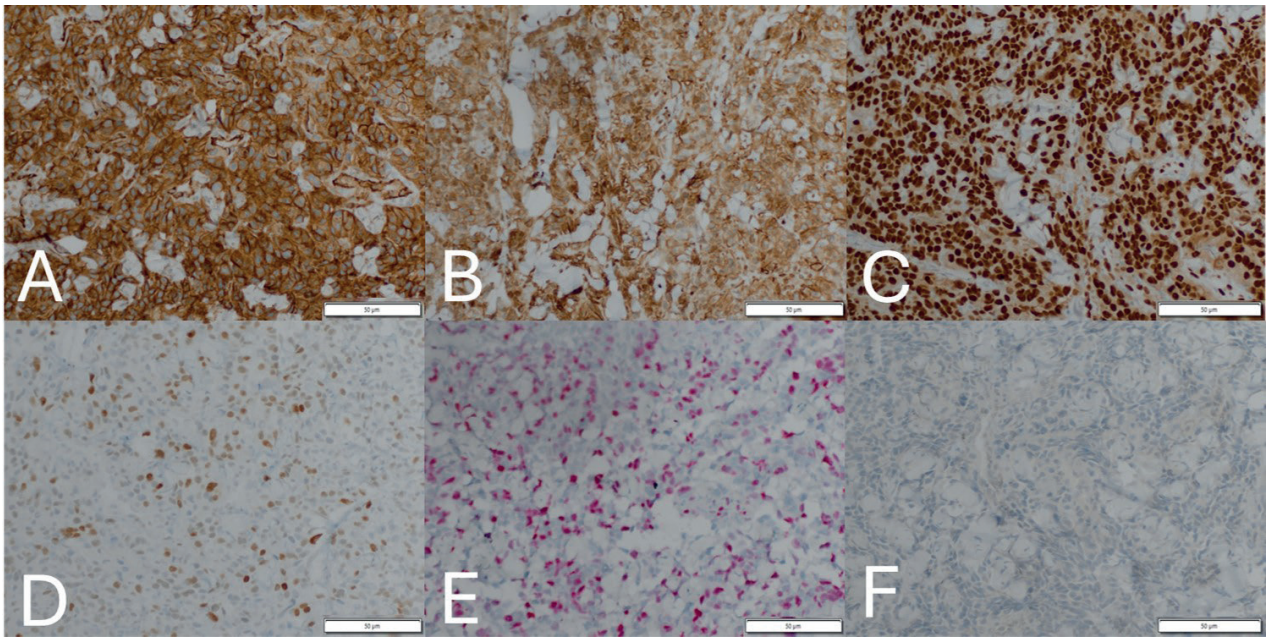

Fig. 3. Immunohistochemistry showed strong cytoplasmic positivity for (A) CD31 and (B) D2-40, along with strong nuclear positivity for (C) ERG and (D) c-Myc. Ki-67 staining indicated (E) an elevated proliferative index of 50–60%, while (F) cytokeratin 20 (CK20) was negative; (A–F) original magnification 200x, bar=50 μm.

evaluation in differentiating between recurrent Merkel cell carcinoma and secondary malignancies, such as post-radiation angiosarcoma. Multidisciplinary collaboration, particularly between dermatologists and dermatohistopathologists, is essential for achieving accurate diagnosis and effectively managing complex oncologic cases (2–4).

Another reason this case draws particular attention is that radiotherapy-associated angiosarcomas are exceedingly rare in male patients. This is primarily due to the fact that they mainly occur after radiotherapy of breast cancer, for which men have a very low prevalence (11). Hardly any cases of other localizations have been described in the literature. Documented cases include angiosarcoma of the small intestine following radiotherapy (12) and angiosarcomas and rhabdomyosarcomas induced by cardiac radiation (13). To our knowledge, this is the first described case of radiation-induced angiosarcoma occurring after radiotherapy of Merkel cell carcinoma. As radiation is often part of its treatment, it is important to keep radiation-induced angiosarcomas in mind during follow-up as a possible late consequence so that they can be adequately identified and treated. Giving its poor prognosis, early analysis using immunohistochemical staining and careful clinicopathological correlation is crucial to ensure rapid diagnosis and appropriate treatment.

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The patient's written informed consent was obtained regarding the publication of their medical records and images.

The authors have no conflicts of interests to declare.

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