CLINICAL REPORT

Synchronous Angiosarcoma, Melanoma and Morphea of the Breast Skin 14 years After Radiotherapy for Mammary Carcinoma

Vincenzo DE GIORGI1, Raffaella SANTI2, Marta GRAZZINI1, Federica PAPI1, Alessia GORI1, Susanna ROSSARI1, Daniela MASSI2 and Torello LOTTI1
Departments of 1Dermatology and 2Human Pathology and Oncology, University of Florence, Florence, Italy

With the improvement in survival after breast cancer there has been increasing interest in the long-term effects of radiotherapy, including the development of tumours. Compared with the general population, breast cancer survivors have a 10–50% higher risk of developing a second cancer. Radiotherapy may play a role in the onset of such lesions. We describe here the case of a 68-year-old woman who developed synchronous cutaneous angiosarcoma, melanoma and morphea of the breast skin and the local area, 14 years after radiotherapy for breast carcinoma. Given the risk of post-radiation secondary primaries in breast cancer patients, long-term surveillance is necessary, with particular attention being paid to skin changes in the irradiation field. Radiation-induced morphea is a rare complication in which immunological abnormalities may stimulate malignant transformation. Long-term studies are required to clarify the pathogenesis of these rare associations. Key words: angiosarcoma; morphea; melanoma; breast; radiotherapy.

(Accepted December 22, 2009.)

Acta Derm Venereol 2010; 90: 283–286.

Vincenzo De Giorgi, Department of Dermatology, University of Florence, Via della Pergola 60, IT-50121 Florence, Italy. E-mail: vincenzo.degiorgi@unifi.it, vdegi@tin.it

With the improvement in survival after breast cancer there is increasing interest in the long-term effects of radiotherapy, including the development of tumours. Compared with the general population, breast cancer survivors have a 10–50% higher risk of developing a second cancer. Radiotherapy may play a role in the onset of such lesions (1–3). Although rare, radiotherapy is associated with an increased risk for subsequent tumours of the skin, including basal cell carcinoma and squamous cell carcinoma, while induction of melanoma has been reported infrequently (4).

Angiosarcoma (AS), a rare cutaneous malignant tumour, was identified as a distinct clinical entity by Wilson Jones in 1964 (5). AS occurs in three specific clinical settings: the head and neck, lymphoedematous limbs in the context of Stewart–Treves syndrome, and irradiated skin areas. Lymphoedema-associated, as well as radiotherapy-associated AS, are more frequently encountered in women patients treated for breast carcinoma (6).

AS of the head and neck usually affects elderly male subjects (age range 59–92 years); its onset is characterized by erythematous-purplish maculae on sun-exposed skin of the forehead and the capillitium, with subsequent rapid growth and metastatic dissemination through the bloodstream (6). Stewart–Treves syndrome is defined by the association of AS developing on long-standing extremity oedema, which more often appears after a radical mastectomy and axillary lymph node dissection for breast carcinoma. The third type of AS occurs in the setting of breast-conserving surgery followed by radiotherapy, developing in the skin of the preserved mammary area within the field of irradiation. The latency period after radiotherapy is variable, from 12–192 months (7, 8). This form of AS is not usually associated with lymphoedema, either in the mammary area or at the level of the upper ipsilateral limb.

We describe here a woman who developed synchronous cutaneous AS, melanoma and morphea of the breast skin and the local area, 14 years after radiotherapy for breast carcinoma.

CASE REPORT

A 68-year-old Caucasian woman presented to our outpatient service with a pigmented skin lesion on her left breast. Past medical history revealed no family history of malignant melanoma and negative anamnesis for skin tumours. Approximately 14 years previously she had undergone breast-conservative surgery and axillary lymph node dissection for an infiltrating ductal carcinoma of the outer lower quadrant of the left breast. At tumour staging, there was no evidence of distant metastases and no lymphoedema on the patient’s left arm. She underwent local radiotherapy (50 Gy, 36 fractions in 3 months) but received no other adjuvant therapy. The following 14 years was a period of relative well-being for the patient, who had regular clinical and instrumental controls (chest X-ray, abdominal ultrasound). She presented with the recent appearance of a growing pigmented lesion on the left breast, within the same area as prior radiotherapy. Clinical examination showed an irregular pigmented lesion with partial
regression, measuring 0.8 × 0.6 cm, with indistinct "fuzzy" limits and irregular margins (no picture). In addition, there were ring-shaped cutaneous patches with a slightly lighter and atrophic centre and a slightly infiltrated red-purplish border in the periareolar region (Fig. 1A). Some areas presented purpuric elements; some patches tended to be confluent. The lesions had appeared some months before and had slowly grown, without any significant subjective symptoms. At the same site, clinical examination revealed the presence of an ivory-coloured plaque of fibrous consistency with a smooth and shiny surface (Fig. 1B). This lesion was asymptomatic and developed at the same time as the erythematous lesions.

The pigmented lesion presented clinical and dermoscopic features that were suspicious for cutaneous melanoma and therefore excisional biopsy was carried out. Two punch biopsies (6 mm) were performed on a ring-shaped erythematous patch and on the ivory plaque, with a clinical diagnosis of granuloma annulare and morphea, respectively.

Histopathological examination of the pigmented lesion showed a poorly circumscribed proliferation of epithelioid and spindle-shaped atypical melanocytes (HMB-45+ and Melan-A+) distributed mostly in single units with focal pagetoid spread within the epidermis, with features of regression. The diagnosis of superficial spreading in situ melanoma was made. Excisional margins were negative. Histopathological examination of the punch biopsy performed on the erythematous ring-shaped patch showed diffuse sclerosis in the dermis (Fig. 2A and B) which was regarded as consistent with the clinical diagnosis of morphea. In addition, irregular, angulated, thin-walled vascular channels scattered throughout the entire dermis were also detected (Fig. 2C). Histopathological examination of the ivory plaque was remarkable for the presence of irregularly angulated and slit-like vascular channels lined by markedly atypical endothelial cells and the infiltrating pattern of growth that dissected dermal collagen bundles were considered in support of a final diagnosis of well-differentiated cutaneous AS (Fig. 3). Immunohistochemistry revealed tumour cells CD31+, CD34+ and D2-40+.

The subsequent left mastectomy specimen confirmed the presence of a widespread well-differentiated cutaneous AS. No extension into the subcutaneous tissue or to the underlying breast parenchyma was observed. Surgical margins were negative. The patient was alive with no evidence of disease at 24 months follow-up. The patient did not subsequently develop morphea involving several sites, and did not have a prior history or went on to develop systemic sclerosis.

DISCUSSION

Following radiotherapy for breast cancer, patients may experience early acute adverse effects such as oedema, erythema, desquamation, and drying of the skin, as well as late complications, including hyperpigmentation, telangiectasias, fibrosis/sclerodermatous changes and tumours, which can occur at any time from months to many years after therapy.

In our case, we observed the unique synchronous association of AS and morphea, two rare complications of breast cancer conservative treatment; both involving the same mammary area 14 years after radiotherapy. In addition, the patient developed a cutaneous melanoma at the same time and in the same irradiated area.

AS of the breast accounts for 0.04% of all malignant tumours of the breast (9, 10). Female breast primary AS is extraordinarily rare (reported incidence less than 0.0005%) (11), while secondary AS is more frequent, its incidence ranging from 0.05% to 0.16% (12). Our case meets all the established requirements of secondary AS (13): a previous history of radiation in the same area in

![Fig. 1. A. Ring-shaped patches on the skin of the left breast, with a slightly lighter atrophic centre consistent with morphea, and a slightly infiltrated red-purplish border with some patches tending to be confluent. Some areas also present purpuric elements. B. Detail of A shows an ivory-coloured plaque of fibrous consistency with a smooth, shiny surface and slight desquamation among the red-purplish lesions of the angiosarcoma.](image-url)
Long-term effects of breast cancer radiotherapy

which the sarcoma arises, a relatively long (more than 10 years) latency period between radiation therapy and diagnosis, and the fact that the new tumour is pathologically distinct from the primary malignancy.

Our patient also developed radiation-induced morphea, a rare complication of breast irradiation (approximately one out of 500 patients) (14). Damage to endothelial cells and fibroblasts following radiotherapy as well as an abnormal immune response mediated by T lymphocytes with subsequent increased collagen production mediated by fibrotic and inflammatory cytokines have been advocated in the pathogenesis of this condition (15, 16). In our case, at histopathological examination we observed a diffuse dermal sclerosis with lack of adnexal structures, consistent with morphea. Although old morphea patches may histologically overlap with chronic radiodermatitis, the clinical features (well-demarcated plaque with an erythematous border rather than as diffuse cutaneous thickening) and onset (abrupt rather than gradual) favoured a diagnosis of localized scleroderma.

Interestingly, in the same skin biopsy in which the diagnosis of morphea was made, we observed vascular changes suggestive of so-called atypical vascular lesions (AVL) of irradiated skin. AVL were present in a skin biopsy close to the area where AS was detected. Although currently regarded as benign conditions, in line
with our observation, AVL have been reported adjacent to frank AS, thus suggesting a possible role of these lesions as a precursor or as the earliest manifestation of cutaneous AS (17–19).

The pathogenesis of cutaneous AS remains unknown, but it has been hypothesized that the malignant transformation begins with over-expression of vascular endothelial growth (VEGF) in the presence of p53 mutation in endothelial cells (20, 21). We may speculate that, in our patient, immunological disturbance in morphea was a potential causative factor in the malignant transformation. Damage to the endothelial cells may initiate the fibrotic process, either through the effects of ischaemia or through growth-modulating mediators released from damaged or activated endothelium and inflammatory cells. In agreement with this hypothesis, three patients who developed AS in the presence of cutaneous lesions clinically and histologically diagnosed as morphea have been previously reported (16, 22). Of these three cases, two, like our patient, had previously received radiotherapy for breast cancer; the third case concerned a woman affected by sclerodermatous skin treated for approximately 6 weeks with low dose of perioral corticosteroid and azathioprine (16, 18). The impaired immunological condition in systemic sclerosis and immunological modifications status due to radiotherapy could be contributing factors in malignant alteration.

Although the induction of melanocytic tumours is a rare event, the association of breast cancer and melanoma has been described, possibly related to a susceptibility gene in parents or certain inherited mutations in genes such as CDKN2A 113insArg. However, despite lack of published evidence, we hypothesize that current breast cancer treatments, such as radiotherapy, may enhance mutations in melanocytic cells of the breast area and subsequently lead to the occurrence of skin melanoma. Experimental studies indicate that gamma-irradiation induces DNA damage, altered cell cycle regulation, activation or suppression of the transcription machinery, and the downregulation of enzymes such as topoisomerase I, which appear to be necessary for DNA repair (23).

In conclusion, given the risk of post-radiation secondary primaries in breast cancer patients, long-term surveillance is necessary, with particular attention on the skin changes in the irradiation field. Radiation-induced morphea is a rare complication in which immunological abnormalities may potentially stimulate malignant transformation. Long-term studies are required to clarify further the pathogenesis of these rare associations.

REFERENCES

1. Rubino C, de Vathaire F, Diao I, Shamsaldin A, LE MG. Increased risk of second cancers following breast cancer: role of the initial treatment. Breast Cancer Res Treat 2000; 61: 183–195.
2. Volk N, Pompe-Kirn V. Second primary cancers in breast cancer patients in Slovenia. Canc Caus Control 1997; 8: 764–770.
3. Doherty MA, Rodger A, Langlands AO, Kerr GR. Multiple primary tumours in patients treated with radiotherapy for breast cancer. Radiother Oncol 1993; 26: 125–131.
4. Trefzer U, Milling A, Audring H, Sterry W. Malignant melanoma arising in radiotherapy field: report of two cases and review of the literature. Dermatology 2003; 206: 265–268.
5. Weedon D. Skin pathology. Edinburgh: Churchill Livingstone, 2002: p. 1001–1043.
6. Weedon D, LeBoit P, Burg G. Sarasinavirais A. World Health Organization classification of tumors. Pathology and genetics of tumours of the skin. Lyon, France: IARC Press; 2005.
7. Huertier C, Kunkel JR, Rouse JR. Angiosarcoma of the face and scalp. Cutis 1993; 51: 461–462.
8. Fink-Puches R, Smolle J, Beham A, Kerl H, Soyer HP. Cutaneous angiosarcoma. Hautarzt 2000; 51: 479–486.
9. Nakamura R, Nagashima T, Sakakibara M, Nakano S, Tanabe N, Fujimoto H, et al. Angiosarcoma arising in the breast following breast-conserving surgery with radiation for breast carcinoma. Breast Cancer 2007; 14: 245–249.
10. Hunter TB, Marteen PM, Dietzen CD, Tyler LT. Angiosarcoma of the breast: two case reports and a review of the literature. Cancer 1985; 56: 2099–2106.
11. Strohbe L, Peterse JL, van Tinteren H, Wijnmaalen A, Rutgers EJT. Angiosarcoma of the breast after conservation therapy for invasive cancer, the incidence and outcome. Breast Cancer Res Treat 1998; 47: 101–109.
12. Zacchini R, Merson M, Placcuci M, Di Palma S, Veronesi U. Soft tissue sarcoma of the breast after conservative surgery and irradiation for early mammary cancer. Radiother Oncol 1994; 30: 271–273.
13. Cahan WG, Woodward HQ, Higginbotham NL, Stewart SW, Coley BL. Sarcoma arising in irradiated bone: report of eleven cases. Cancer 1948; 1: 3–29.
14. Davis DA, Cohen PR, McNee MD, Duvic M. Localized scleroderma in breast cancer patients treated with supervalve external beam radiation: radiation port scleroderma. J Am Acad Dermatol 1996; 35: 923–927.
15. Dubner S, Bovi I, White J, Susnik. Postirradiation morphea in a breast cancer patient. Breast J 2006; 2: 173–176.
16. Schaffier JV, Carroll C, Dvoretsky I, Huehner MJ, Girardi M. Postirradiation morphea of the breast: presentation of two cases and review of the literature. Dermatology 2000; 200: 67–71.
17. Gengler C, Coindre JM, Leroux A, Trassard M, Ranchère-Vince D, Valo I, et al. Vascular proliferations of the skin after radiotherapy therapy for breast cancer: clinicopathological analysis of a series in favour of a benign process. A study from the French Sarcoma Group. Cancer 2007; 109: 1584–1598.
18. Requena L, Kutzner H, Mentzel T, Durán R, Rodriguez-Peralto JL. Benign vascular proliferations in irradiated skin. Am J Surg Pathol 2002; 26: 328–337.
19. Brenn T, Fletcher CD. Radiation-associated cutaneous atypical vascular lesions and angiosarcoma: clinicopathological analysis of 42 cases. Am J Surg Pathol 2005; 29: 983–996.
20. Puizina-Ivcevic N, Bezie J, Marasovic D, Gotovac V, Carija A, Bozic M. Angiosarcoma arising in sclerodermatous skin. Acta Dermatovenerol Alp Panonica Adriat 2005; 14: 20–25.
21. Arbiser JL, Larsson H, Claesson-Welsh L, Bai X, LaMontagne K, Weiss SW, et al. Overexpression of VEGF 121 in immortalized endothelial cells causes conversion to slowly growing angiosarcoma and high level expression of the VEGF receptors VEGFR-1 and VEGFR-2 in vivo. Am J Pathol 2000; 156: 1469–1476.
22. Beco J, DeKoven J, Beaty J, Joens G. Cutaneous angiosarcoma as delayed complication of radiation therapy for carcinoma of the breast. J Am Acad Dermatol 2003; 49: 532–538.
23. Boothman DA, Burrows HL, Yang CR, Davis TW, Wuerzberger SM, Planchnon SM, et al. Damage-sensing mechanisms in human cells after ionizing radiation. Stem Cell 1997; 15: 27–42.