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Case and Review

Post-Irradiation Morphea of the Breast in a Patient with Subacute Cutaneous Lupus Erythematosus: Case Report and a Literature Review

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Keywords
Morphea · Post-irradiation · Autoimmunity · Breast · Lupus erythematosus

Abstract
The appearance of morphea after radiotherapy, especially in the context of breast cancer, is a rare but known phenomenon. The incidence of post-irradiation morphea (PIM) of the breast is approximately one in every 500 patients, a higher rate than morphea of any other etiology, which is three per 100,000 per year. PIM usually appears less than 1 year after irradiation (range 1 month to 32 years). The histological pattern of PIM is different from the one in post-irradiation fibrosis, which is a common side effect of radiotherapy and usually appears during the first 3 months after irradiation. Several theories have been proposed to explain the pathogenesis of PIM, probably caused by a disturbance of the cytokine pattern. The development of PIM in patients with autoimmune diseases has been described in the literature. To our knowledge, we report the first case of PIM in a patient with subacute cutaneous lupus erythematosus. We should therefore pay attention when looking at patients with PIM to search for an underlying autoimmune disease.

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Introduction

Radiation-induced morphea is a rare, but well-described, disfiguring disease with a negative impact on the patient's quality of life [1]. Following the description of the first case in 1989 [2], other cases were reported, mostly in female patients after diagnosis of breast cancer. The development of PIM in patients with autoimmune diseases has been described in the literature [1, 3]. We present a case of post-irradiation morphea (PIM) of the breast in a patient with subacute cutaneous lupus erythematosus (SCLE) and a review of the literature.

Case Report

A 58-year-old woman developed reddish-papular infiltrated lesions on the upper back. An SCLE, characterized by erythematous annular patches and plaques on the trunk, was diagnosed based on the clinical presentation, the histological findings of lichenoid dermatitis, and positive anti-Ro/SSA antibodies (10.0 multiples of cutoff; normal <1.0). After treatment with hydroxychloroquine 200 mg twice daily and topical tacrolimus unguent, the skin lesions resolved rapidly. We reduced the daily dose to 200 mg daily and the disease remained in remission under treatment for the following 10 years.

At age of 68-year-old, the patient was operated on for a mucinous cancer of the left breast (27 mm, cT2, cN1sn [1/4], cM0, G3, ER 80%, PR 20%, Ki-67 15%, c-erB-2 score 0). The procedure was completed with an axillary lymphadenectomy, a radiotherapy (total dose 60 Gy), and a pharmacological treatment with letrozole and tamoxifen.

After 6 months, the patient developed an erythema of the left axillary region. The skin lesions on the left axillary region and lateral breast persisted for a year despite topical corticosteroid treatment. Histology showed interstitial granulomatous dermatitis. Clinical activity fluctuated over the next years between less and more inflammatory aspects, though never disappearing under topical corticosteroid treatment.

Six years after appearance of the axillary lesions, a novel induration appeared on the tumor scar. Reddish to slightly violaceous patches, which spared the nipple on the left breast, appeared simultaneously (Fig. 1). Histology showed a flattened epidermis, dermal edema with homogeneous and eosinophilic collagen fibers, and a scanty perivascular and diffuse infiltrate of lymphocytes and plasma cells, compatible with morphea (Fig. 2a, b). A tissue PCR testing and a serology for *Borrelia burgdorferi* were negative. The patient decided not to treat the morphea with any specific medication, except emollients and during the following 18 months, while the morphea persisted, the SCLE stayed in remission.

Discussion

The incidence of PIM of the breast is approximately one in every 500 patients, a higher rate than morphea of any other etiology, which is three per 100,000 per year [4]. PIM usually appears less than 1 year after irradiation (range 1 month to 32 years, according to the literature) [4, 5]. A PubMed search for cases of PIM published to date revealed 46 cases of female patients with breast cancer (Table 1) [4, 6–24]. The histological pattern of PIM is different from post-irradiation fibrosis, which is a common side effect of radiotherapy and usually appears during the first 3 months after irradiation [1]. Despite various hypotheses, the exact pathogenesis of morphea still remains unclear. It seems, however, that a disturbance of the cytokine pattern plays an important role in the development of the disease [1, 25–30]. Radiotherapy increases collagen synthesis, which boosts the secretion of Th2 cytokines

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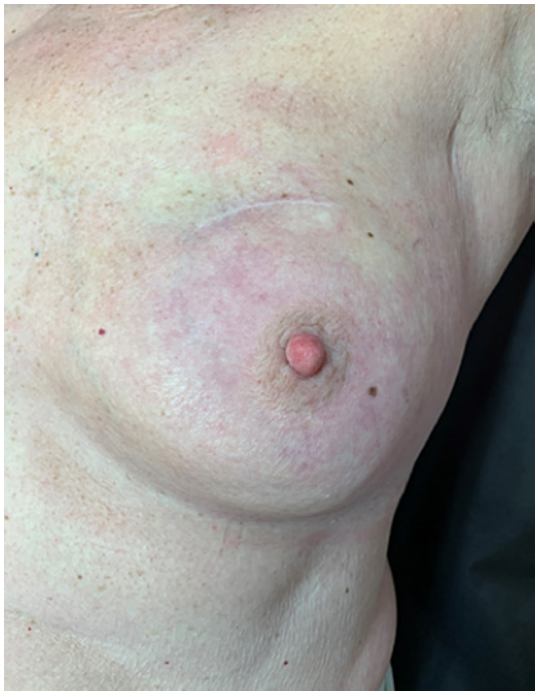

Fig. 1. Reddish to slightly violaceous patches which spared the nipple on the left breast.

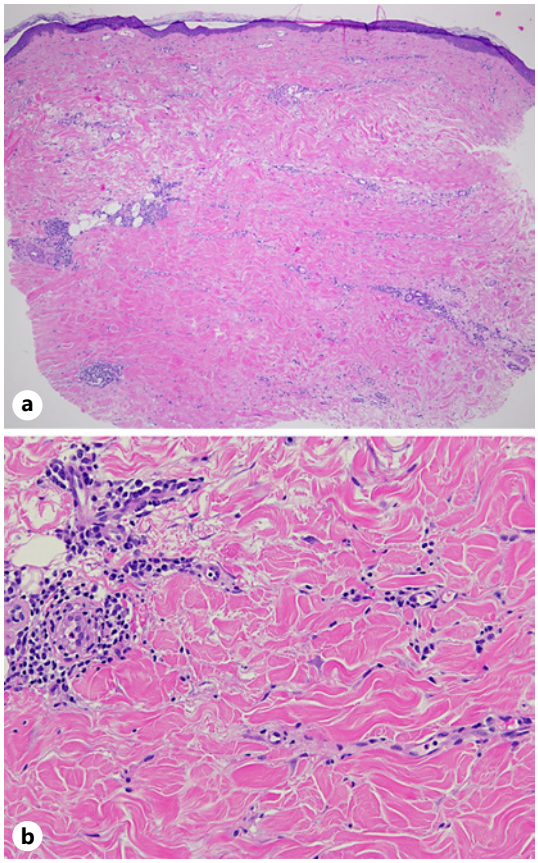

Fig. 2. a Histological overview of dermal fibrosis (HE) – magnification, ×40. **b** Histological detail of chronic dermatitis, numerous plasma cells, and a dermal fibrosis (HE) – magnification, ×200.

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Table 1. Series of 47 case reports of radiation-induced morphea after breast carcinoma described in the literature with our case

References	Cases, *n*	Publication year	Mean age of patients, years	Radiation dose, Gy	Latency period between radiation and skin disease onset, months	Auto-antibodies laboratory results	Treatment
Colver et al. [2]	7	1989	61	43–59	18–120 (mean 42)	NR	NR
Forbes et al. [9]	1	1989	57	NR	1	ANA-	NR
Robertson et al. [10]	2	1991	60	50.4	8–11	NR	NR
Trattner et al. [11]	1	1991	57	50	<12	ANA+ (1/320)	NR
Winkelmann et al. [12]	4	1993	68	46–50	1–6	NR	NR
Davis et al. [13]	6	1996	52	46–55	<12	ANA-	Topical, intralesional and systemic CS therapy
Mayr et al. [14]	1	1997	NR	NR	<12	NR	NR
Gollob et al. [15]	1	1998	54	42.5	4	NR	Topical CS
Bleasel et al. [16]	4	1999	60	45–50.4	<12	NR	Topical CS under occlusion
Fischer et al. [17]	1	1999	74	NR	108	NR	Photopheresis with hyaluronidase and PUVA
Schaffer et al. [26]	2	1999	65	43–46	79–382	ANA+ (1/640) and ENA-	1st patient with topical CS and oral doxycycline; 2nd patient no treatment
Arden-Jones and Black [18]	1	2003	60	NR	156	NR	Methotrexate 2.5 mg/week
Ullen and Björkholm [19]	1	2003	67	50	<12	NR	NR
Reddy et al. [20]	1	2005	75	NR	<12	NR	Systemic CS
Dubner et al. [5]	1	2006	52	50.4	36	NR	Mastectomy refused from patient
Dancey et al. [38]	2	2006	60	NR	<12	NR	NR
Seale et al. [21]	1	2008	60	NR	24	NR	NR
Walsh et al. [8]	5	2008	58	NR	48–144	NR	Potent topical CS; other had mastectomy
Cheah et al. [7]	1	2008	69	NR	9	NR	Topical and oral CS and PUVA
Herrmann et al. [22]	1	2009	85	NR	18	NR	NR
Morganroth et al. [23]	1	2010	64	NR	NR	NR	NR
Alhathlool et al. [24]	1	2011	64	NR	24	NR	Penicillin, topical calcipotriol, and UVA1 radiation
Our case	1	2021	75	60	72	ANA+ (1/80), Anti-Ro/SSA+ (>240.0 U/mL)	Patient refused treatment

NR, not reported; ANA, anti-nuclear antibodies; CS, corticosteroids; PUVA, psoralen and ultraviolet A radiation.

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Table 2. Adverse effects of radiotherapy on the skin

Acute adverse effects	Late adverse effects
Erythema	Erythema
Edema	Hyperpigmentation
Desquamation	Telangiectasia
	Skin tumors: Basal cell carcinoma Squamous cell carcinoma Malignant melanoma Angiosarcoma
	Sclerodermatous changes such as morphea

(IL-4 and IL-5) [1]. This phenomenon has already been described in animal models, where a TGF-b1 elevation and a significant skin fibrosis followed mice irradiation [28]. Also, human in vivo studies showed an indurated skin and a higher collagen production after irradiation compared with non-irradiated skin [29].

Besides genetic predisposition, prior viral infections (Epstein-Barr virus, varicella-zoster virus) and bacterial infections (*Borrelia burgdorferi*), as well as surgery or any other type of local trauma can trigger morphea [5]. Morphea occurs like psoriasis especially at "sites of trauma in a genetically predisposed person," as defined by the isomorphic phenomenon of Koebner [31, 32]. Possible trauma also includes radiotherapy, which seen for itself in rare cases can increase the risk for development of skin tumors [33, 34]. Table 2 summarizes frequent possible secondary effects of radiotherapy on the skin.

Morphea coexists in some patients with underlying autoimmune diseases such as Hashimoto's thyroiditis, vitiligo, primary biliary cirrhosis, autoimmune hepatitis, myasthenia gravis, or multiple sclerosis, mostly in the generalized and mixed subtypes with a higher prevalence among adults (29%) than children (3%) [32, 33, 35]. Besides extracutaneous manifestations such as arthritis, joint contractures, myositis, fasciitis, neurologic, ophthalmologic, and dental issues, half of the patients analyzed in the cohorts showed autoantibody positivity. The severity of the extracutaneous manifestations correlates with autoantibody titers [25]. Autoimmune diseases may predispose to morphea and PIM.

Due to the partially unclear pathogenesis, targeted treatment remains difficult. Some case reports suggest a "watch and wait" attitude, as the skin lesions may resolve spontaneously [36, 37]. In mild forms, topical or systemic steroid application in combination with methotrexate may already lead to an adequate benefit. In other cases, oral antibiotics, topical calcineurin inhibitors (tacrolimus), or imiquimod are required [7]. Phototherapy, especially psoralen and ultraviolet A radiation and UVA1, have shown a significant reduction of TGF-b, which led to a softening of the skin texture [6].

In cases of intractable local breast pain, mastectomy may have to be considered [8–10]. In conclusion, to our knowledge, we report the first case of PIM in a patient with SCLE.

Statement of Ethics

Research complies with all ethical guidelines for human studies and animal welfare regulations. Ethical approval was not required for this study in accordance with local guidelines. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

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Conflict of Interest Statement

The authors declare that there are no conflicts of interests to disclose.

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Author Contributions

Carole Anouk Zahn and Carlo Mainetti contributed to conception and design of the case report. Laurence Feldmeyer and Roland Blum performed the histological analysis. Carole Anouk Zahn wrote the first draft of the manuscript. Carole Anouk Zahn, Carlo Mainetti, Laurence Feldmeyer, and Roland Blum contributed to manuscript revision, read, and approved the submitted version.

Data Availability Statement

The authors confirm that the data supporting the findings of this study are available within the article. Further inquiries can be directed to the corresponding author.

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