Morphea in Post-irradiated Skin of a 65-year-old Female with Breast Cancer: A Case Report and Review of the Literature and Treatment Options

Mayha Patel, DO,* Teresa Ishak, DO,** John Merrill, BS,*** David Horowitz, DO, FAOCD****

*Dermatology Resident, 2nd year, Chino Valley Medical Center/Western University, Chino, CA
**Dermatologist, Private Practice, Fullerton, CA
***Medical Student, 3rd year, Western University of Health Sciences College of Osteopathic Medicine, Pomona, CA
****Faculty, Dermatology Residency Program, Chino Valley Medical Center/Western University, Chino, CA

Abstract
Morphea is a localized form of scleroderma presenting with sclerotic erythematous plaques limited to the skin with no internal organ involvement. A specific type of morphea called post-irradiation morphea occurs in patients one month to three years after radiation treatment. This is a very rare and under-recognized condition that is often misdiagnosed. We report the case of a 62-year-old female with post-irradiation morphea and review the pathogenesis and treatment options in addition to its similarities and differences with radiation-induced fibrosis.

Introduction
Morphea, or localized scleroderma, is a localized, cutaneous form of scleroderma that lacks the systemic features and organ involvement characteristic of progressive systemic scleroderma. It typically presents as a violaceous to hypopigmented plaque that progresses to induration with a smooth and shiny surface as sclerosis develops. Possible etiologic triggers of morphea include traumatic injury, infection, chemical exposure, and radiation exposure. The incidence of morphea of any etiology in the general population is 2.7 per 100,000 per year.1

Post-irradiation morphea (PIM) is a rare condition that appears abruptly with erythema and induration followed by fibrosis in women one month to three years status post-radiation treatment of breast cancer.1 The first case of morphea as a complication of radiotherapy for cancer was reported by Colver et al. in 1989.2 Since then, several cases of PIM have been reported, and the incidence of PIM is estimated to be approximately 1 in 500 patients.2

Radiation-induced morphea (RIM) of the breast should be distinguished from PIM. RIM occurs anywhere from one to 12 months, and possibly up to 32 years, after radiation therapy.3 In addition, the involved area of PIM typically correlates with a previous radiotherapy treatment field, whereas in RIM, involvement is always seen both within and beyond the radiotherapy field.4

We report a case of post-irradiation morphea (PIM) following local irradiation of breast cancer and review the various treatment approaches found in the literature.

Case Report
A 62-year-old female was diagnosed with breast cancer in June of 2008 and immediately sent for lumpectomy and sentinel lymph node dissection on July 2, 2008. All nodes were negative during this procedure. The patient then underwent radiation therapy from October to November of 2008, five days a week for seven weeks. After this therapy, the patient was started on tamoxifen but was only able to tolerate about two months of treatment due to side effects. She discontinued this medication and made the decision not to continue with any systemic treatment. The patient had an uncomplicated period of two years from the cessation of her therapy in 2008. However, in 2010 she began to develop thickening of the skin under her left and right breast in addition to multiple erythematous lesions under bilateral breast folds. The patient was subsequently referred to our dermatology clinic by her oncologist, who was concerned the rash may be evidence of metastatic carcinoma.

On clinical exam, the patient had multiple blanchable, sclerotic, erythematous, palpable plaques under her bilateral breast folds (Figures 1, 2). A punch biopsy was consistent with morphea, showing thickened collagen bundles in the reticular dermis and superficial subcutaneous adipose tissue and a superficial and deep perivascular and interstitial lymphoplasmacytic infiltrate (Figure 3). The patient was started on clobetasol ointment applied once daily, with significant improvement.

Discussion
Post-irradiation morphea was first described in 1905 as a condition that develops after exposure to radiographs.5 However, it was not until 1989 that Colver et al. recognized PIM as a complication of radiotherapy for cancer.2 There has been no published data on the risk factors involved in the development of PIM nor on a linear relationship to radiation dose.4 One proposed theory for the development of PIM is that radiation exposure may activate clonal fibroblasts, resulting in autoimmunity. An increase in cytokine production, such as transforming growth factor-β (TGF-β), has been found.6 This response results in an increase in glycosaminoglycan production, collagen synthesis and extracellular matrix protein secretion. TGF-β is secreted by platelets, macrophages and T-lymphocytes, and an increase in the binding of platelet-derived growth factor (PDGF) to scleroderma fibroblasts has been observed after TGF-β expression. This binding of PDGF leads to an increased growth of scleroderma fibroblasts.1 Another study proposes the theory that these radiation-induced neoantigens that occur through direct effects on cellular proteins are recognized months to years later by B and T cells.7 This recognition produces a local inflammatory response that results in the release of growth factors and other cytokines that go on to stimulate the production of excess collagen by fibroblasts.

PIM is commonly misdiagnosed as radiation-induced fibrosis (RIF), which is a much more common condition, believed to occur in about 23% of breast cancer patients given radiation treatment.4 There are several differences between

Figure 1

Figure 2

Figure 3
PIM and RIF. On histology, RIF lacks an inflammatory infiltrate and is primarily a deep subcutaneous and fascial fibrosis, whereas PIM is a localized scleroderma of primarily dermal fibrosis. PIM occurs one month to three years after radiation exposure, whereas RIF usually occurs in the first three months after treatment. In addition, PIM is often abrupt in onset, with erythema and induration seen in the first phase of the condition, which is not observed in RIF. Finally, PIM usually begins within the field of radiation and in about 20% of cases may extend beyond that field, while RIF does not spread past the radiation site. The different histologic and clinical findings of PIM and RIF are summarized in Table 1.

**Table 1. Histologic and clinical findings of PIM and RIF**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Clinical Findings</th>
<th>Etiology</th>
<th>Histology</th>
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| Post-irradiation Morphea (PIM) | - Abrupt onset  
- Two phases:  
  1. inflammatory: erythema, induration  
  2. “burnt-out”: induration, fibrotic retraction, pigmentation  
- Primarily a dermal fibrosis  
- Occurs 1 month to 3 years after exposure  
- Can expand beyond the field of radiation exposure | - Radiation-induced neoantigen  
- Neoantigen later recognized by B and T cells, stimulating TGF-β  
- TGF-β strongly induces fibroblast activation, collagen synthesis, excessive fibrosis  
- PDGF binds to scleroderma fibroblasts, causing increased fibroblast growth | - Thickened collagen bundles in reticular dermis and superficial subcutaneous adipose tissue  
- superficial and deep perivascular and interstitial lymphoplasmacytic infiltrate in subcutaneous tissue underlying breast tissue |
| Radiation-induced Fibrosis (RIF) | - More common  
- Occurs within 3 months of exposure  
- Primarily a deep subcutaneous and fascial fibrosis  
- No erythema or induration  
- Does not expand beyond the field of radiation exposure | - Overactive signaling via PDGF receptor beta and V-abl Abelson murine leukemia viral oncogene homolog 1 (cAbl) | - Little or no inflammatory infiltrate  
- Differentiation of fibroblasts into postmitotic fibrocytes  
- Changes in vascular connective tissue  
- Excessive production and deposition of extracellular matrix proteins and collagen |

**Table 2. Therapeutic options for PIM**

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<tr>
<th>Medication</th>
<th>Effect on Morphea</th>
<th>Mechanism of Action</th>
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| UVA-1                                   | - Reduction in sclerotic plaques  
- Increase in skin elasticity  
- Decrease in skin thickness as measured by ultrasound | - Levels of MMP-1/2/3 increase after UVA1 treatment  
- Increase in collagenase mRNA and protein expression in fibroblasts  
- Increase in collagen metabolism  
- Increased level of α-melanocyte-stimulating hormone (α-MSH) |
| Combination of calcipotriol ointment with low-dose UVA-1 | - Morphea fibroblasts have an increased sensitivity to vitamin D3 receptors, leading to inhibition of proliferation  
- Positive synergistic interference of both modalities | - Levels of MMP-1/2/3 increase after UVA1 treatment  
- Increase in collagenase mRNA and protein expression in fibroblasts  
- Increase in collagen metabolism  
- Increased level of α-melanocyte-stimulating hormone (α-MSH)  
- Calcipotriol causes an alteration of collagen and fibronectin synthesis as well as inhibition of fibroblast proliferation |
| Tyrosine kinase inhibitor (imatinib)     | - Decrease in skin thickness  
- Decrease in myofibroblast numbers  
- Extracellular matrix accumulation | - Blocks the PDGF receptor and inhibits the TGF-β and PDGF-induced response in fibroblasts |

**Differential Diagnosis**

Other important differential diagnostic considerations include acute, subacute, and chronic radiation dermatitis, sclerosing post-irradiation panniculitis and radiation recall dermatitis, which is the recalling by skin of previous radiation exposure in response to the administration of certain response-inducing drugs.
Histology
In PIM, the sclerosing changes seen clinically are thickened collagen bundles in the reticular dermis and superficial subcutaneous adipose tissue. The inflammatory changes are characterized by a superficial and deep perivascular and interstitial lymphoplasmacytic infiltrate, which is also seen in the subcutaneous tissue and underlying breast tissue.8,9 (Figure 3).

In radiation-induced fibrosis, an enhanced synthesis and deposition of the interstitial collagens, fibronectin and proteoglycans have been seen in fibroblast tissue in addition to differentiation of fibroblasts into postmitotic fibrocytes. These changes are due to radiation-induced modulation of the fibroblast-cell system to an abnormal proliferation of fibroblasts.7,8

Treatment
Mild treatments for early lesions of PIM include topical and intralesional steroid creams and oral antibiotics. High-dose UVA1 treatment for localized scleroderma was first conducted by Stege et al. in 1997.9 They found positive effects in terms of skin thickness and elasticity as well as increased levels of β-melanocyte-stimulating hormone (β-MSH), which would explain the normalization of skin color post treatment.10,11 Medium-dose UVA1 treatment was no less effective than high-dose treatment and was significantly superior to UVB treatment and low-dose UVA1, with effects seen even in darker skin tones. UVA irradiation results in localized immunosuppression and remodeling of dermal collagen as it penetrates deeper into the skin, particularly by induction of matrix metalloproteinases, which are collagenases that initiate the cleavage process of the main collagen found in the skin.

There have been several reports on success of combination treatment with calcipotriol ointment and UVA1 irradiation in the management of morphea. It has been shown that morphea fibroblasts have an increased sensitivity to vitamin D3 receptors, leading to inhibition of proliferation and a positive synergistic interference of both modalities when given in combination. It must be noted, however, that the application of topical calcipotriol should not be performed two hours prior to or after phototherapy so as to avoid adverse interactions with UV radiation.12,13 Other therapeutic options are calcineurin inhibitors, heparin-containing creams and the tyrosine kinase inhibitor imatinib. Imatinib blocks the PDGF receptor and inhibits the TGF-β and PDGF-induced response in fibroblasts, which play a key role in the pathophysiology of PIM.14 In patients who are treated with imatinib, a decrease in skin thickness, myofibroblast numbers and extracellular matrix accumulation is seen.12 Total excision of the area can also be conducted. For extreme cases of severe breast pain, a total mastectomy to alleviate the symptoms is often required. In other patients, the disease can be self-limiting, with spontaneous gradual softening of the skin. The therapeutic options are reviewed in Table 2.

Any treatment modality should be administered promptly to give the best result; however, there is little information on the overall outcome of these treatments in PIM. PUVA therapy itself does not completely reverse fibrosis and atrophy but instead causes distinct skin softening and therefore reduction in pruritus, pigmentation and skin tightness. Most skin changes may be improved within a few months to a few years, but pigmentation usually persists.

Conclusion
Post-irradiation morphea is a rare but potential complication after radiotherapy for cancer. This skin disease occurs months to years after treatment, and is associated with remarkable morbidity and pain as well as cosmetic changes that are often very troublesome to patients. Researchers still do not know the relationship between the dosage of radiation and the severity of the induced morphea. For proper management and treatment, dermatologists and radiation oncologists should be aware that this condition may lead to the mistaken diagnosis of local tumor recurrence.

References


Correspondence: Mayha Patel, DO; mayhapatel@gmail.com