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Radiation-induced morphea: Association with autoimmune comorbidities, severity, and response to therapy

To the Editor: Radiation-induced morphea (RIM) is a rare cutaneous complication of radiation therapy (RT) that is reported mostly in patients with breast cancer.[1-3] Its association with autoimmune disorders is not well established. In this report of 25 cases, we retrospectively analyzed patients' comorbidities, disease severity, and response to treatment.

The electronic medical records at Yale New Haven Hospital, Northwestern Memorial Hospital, and Stanford University (2000-2018) were searched after institutional review board approval to identify patients with a clinical and histologic diagnosis of morphea developing after RT. The inclusion criteria were treatment with RT, clinical diagnosis of morphea developing during or after RT, and histopathologic confirmation of morphea. The exclusion criteria were radiation-induced dermatitis, radiation fibrosis, radiation recall, carcinoma, fat necrosis, panniculitis, and cellulitis/erysipelas. Clinical notes and images were assessed for disease severity and treatment response. Severity was defined by using an adapted version of the modified Localized Scleroderma Skin Severity Index (mLoSSI),[2] according to which skin thickness was assigned 1 point for minimal/localized sclerosis, 2 points for moderate sclerosis, or 3 points for severe/generalized sclerosis. Mild disease was defined as an mLoSSI score less than 6, moderate disease was defined as an mLoSSI score of 6 to 18, and severe disease was defined as an mLoSSI higher than 18. Treatment response was defined as major response (MR) (improvement by at least 1 severity level), partial response (improvement not qualifying as major response), stable response (no progression or improvement in disease), or disease progression (any worsening of lesions). We conducted a comprehensive chart analysis of medical diagnoses, laboratory data, and clinical notes to identify any disease qualifying as autoimmune related.

Coexistent autoimmune disorders occurred in 11 of 25 patients (44%), 10 of whom (90.9%) had severe RIM. Rheumatoid arthritis was most common (n = 6). Further, most patients with a positive (>1:80) antinuclear antibody testing result (7 of 9 patients [77.8%]), obesity (7 of 9 patients [77.8%]), history of former or active smoking (7 of 10 patients [70%]), and breast implantation (4 of 4 patients [100%]) had severe RIM.

Table I summarizes patient characteristics, associated comorbidities, latency of onset, and oncologic treatment regimen.

Clinicopathologic correlation demonstrated a spectrum from inflammatory to burnt-out disease based on the degree of clinically visible erythema.[1] Lesions occurred outside the radiation field in 14 of 25 patients (56%), 3 (21.4%) of whom developed generalized morphea, and 9 (64.3%) of whom had comorbid autoimmune disease. The type and dose of radiation and other oncologic treatments did not correlate with RIM within or outside the radiation field.

Table II summarizes treatment and response to therapy based on disease severity and activity.

Table I. Characteristics of patients with RIM (N = 25)

Characteristic	Value
Sex, n (%)	
Male	2 (8)
Female	23 (92)
Patients with a positive smoking history, n (%)	10 (40)
Mean pack-years (range)	46 (5-90)
Mean age, y (range)	61 (42-77)
Mean body mass index, kg/m^2 (range)	30.0 (17.3-42.1)
Patients with autoimmune disease, n (%)*	11 (44)
Rheumatoid arthritis	6 (24)
Systemic sclerosis	2 (8)
Hashimoto thyroiditis	2 (8)
Other autoimmune disease (1 case each of Graves disease, myositis, ulcerative colitis, and Guillain-Barré syndrome)	4 (16)
Patients with a positive antinuclear antibody result, n (%)	9 (36)
Titer of 1:80	4 (16)
Titer of 1:160	1 (4)
Titer of 1:320	4 (16)
Cancer types, n (%)	
Invasive ductal carcinoma	19 (76)
Other cancer type (1 case each of invasive lobular carcinoma, invasive tubulolobular carcinoma, dendritic cell sarcoma, undifferentiated pleomorphic sarcoma, non−small cell lung cancer, and inflammatory breast cancer)	6 (24)
Surgical procedures, n (%)	
Lumpectomy	8 (32)
Partial mastectomy	9 (36)
Modified radical mastectomy	5 (20)
Breast reduction	1 (4)
Resection	2 (8)
Implant reconstruction	4 (16)
Sentinel lymph node biopsy	3 (12)
Axillary lymph node dissection	6 (24)
Persistent swelling or lymphedema after surgery	4 (16)
No surgery	1 (4)
Radiation	
Mean latency of onset from last radiation treatment, mo (range)	35.1 (3-186)
Mean radiation treatment dose, cGy (range)†	4761 (4005-6000)
Mean radiation boost dose, cGy (range)	1343 (1000-2600)
Patients who received radiation boost, n (%)	14 (56)
Boost with photon radiation	8 (32)
Boost with electron radiation	6 (24)
Patients with RIM within radiation treatment field, n (%)	25 (100.0)
Patients with RIM beyond radiation treatment field, n (%)	14 (56)
Patients with autoimmune disease, n (%)*	9 (64.3)
Lesion distribution, n (%)	
Unilateral breast	23 (92)
Contralateral breast	3 (12)
Ipsilateral inframammary fold/upper abdomen	21 (84)
Ipsilateral flank (lateral upper chest, back, or axilla)	14 (56)
Neck	1 (4)
Thigh	1 (4)
Generalized‡	3 (12)

RIM, Radiation-induced morphea.
*Some patients had multiple autoimmune diseases.
†All patients received photon radiation.
‡Involvement of 2 or more anatomic sites outside the RT field.

Table II. Treatment and response for patients with RIM (N = 25)

Severity and disease activity	Patients, n
Severity	
Mild (mLoSSI, <6), n (%)	2 (8)
Treatment (response)	
Observation	1 (1 SR)
nbUVB + topicals	1 (1 MR)
Moderate (mLoSSI, 6-18), n (%)	6 (24)
Treatment (response)	
Topical	3 (3 PR)
nbUVB + topicals	2 (2 PR)
UVA + MTX/topicals	1 (1 MR)
Severe (mLoSSI, >18), n (%)	17 (68)
Treatment (response)	
Topical	12 (3 SR, 6 PR, 3 MR)
nbUVB + topical	1 (1 SR)
UVA + topical	1 (1 PR)
Prednisone, MTX + topical	1 (1 PR)
Tofacitinib, prednisone, photopheresis, and MTX	1 (1 MR)
MMF, MTX, and celecoxib	1 (1 SR)
Disease activity	
Inflammatory, n (%)	8 (32)
Treatment (response)	
Observation	1 (1 SR)
nbUVB + topicals	1 (1 MR)
Topicals	4 (1 PR, 3 MR)
Prednisone, MTX + topical	1 (1 PR)
Tofacitinib, prednisone, photopheresis, and MTX	1 (1 MR)
Burnt-out, n (%)	17 (68.0)*
Treatment (response)	
Topicals	11 (3 SR, 8 PR)
nbUVB + topicals	4 (1 SR, 3 PR)
UVA + topicals	1 (1 PR)
UVA + MTX	1 (1 MR)
MMF, MTX, celecoxib	1 (1 SR)

mLoSSI, Modified Localized Scleroderma Skin Severity Index); *MMF*, mycophenolic acid; *MR*, major response (improvement by at least 1 severity level); *MTX*, methotrexate; *nbUVB*, narrowband ultraviolet B phototherapy treatment; *PR*, partial response (improvement not qualifying as major response); SR stable response (no progression or improvement in disease); *RIM*, radiation-induced morphea; *UVA*, ultraviolet A phototherapy treatment.
*Some patients had multiple treatment regimens.

Response to therapy varied from disease progression to MR. Of the patients with clinical follow-up, those with inflammatory RIM were more likely to demonstrate MR than were those with burnt-out disease (5 of 8 patients [62.5%] vs 1 of 17 patients [5.9%]; respectively). Most patients responded to combination treatment with topicals (steroids, calcineurin inhibitors, or vitamin D analogues), phototherapy (ultraviolet A or narrowband ultraviolet B), and/or systemic drugs (prednisone, methotrexate, mycophenolic acid, celecoxib, or tofacitinib[4]).

This study of a relatively large cohort of patients with RIM analyzed comorbidities and potential associated risk factors; autoimmune disorders, obesity, smoking history, and breast implantation were correlated with severe disease. A previous study stratifying morphea subtypes demonstrated that approximately 50% of patients with generalized morphea had autoimmune disease,[5] but it did not evaluate those with RIM. A majority (64.3%) of patients with RIM extending beyond the radiation field had autoimmune disease in this cohort. This study is limited by its retrospective nature, and further studies are required to confirm the findings.

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