Observation

Improvement in Dermatomyositis Rash Associated With the Use of Antiestrogen Medication

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Background: Dermatomyositis (DM) is an autoimmune disorder that occurs more often in women than men and causes highly symptomatic and inflammatory cutaneous and proximal muscle disease. Corticosteroids have been the treatment of choice for myositis in DM, and antimalarial agents for the skin disease of DM, with methotrexate sodium, azathioprine, mycophenolate mofetil, cyclosporine, and intravenous immunoglobulin used as steroid-sparing agents. Recently, reports supporting a role for anti–tumor necrosis factor (TNF-α) therapy in the treatment of DM have emerged.

Observations: We describe 2 women who experienced an improvement in their DM-associated skin eruptions while taking antiestrogen medication. The first patient was taking tamoxifen, a selective estrogen receptor modulator that has been found to have anti–TNF-α properties. The second was taking anastrozole, an aromatase inhibitor. When tamoxifen therapy was discontinued after 4 years of use in the first patient, her DM rash worsened and remained difficult to control with conventional immunosuppressant medication.

Conclusions: With the limited number of therapies available to manage DM skin eruptions, the discovery of novel agents effective in treating this disease is vital. Using antiestrogen medication in women with DM may result in a significant improvement in their rash, possibly via the inhibition of TNF-α production by immune or other cells. Further investigation into the use of antiestrogen therapy in DM is merited to evaluate long-term risks and benefits.

Arch Dermatol. 2006;142:70-72

DERMATOMYOSITIS (DM) is an autoimmune disease that primarily targets the skin and limb girdle muscles. In some patients, it manifests exclusively or predominantly as cutaneous disease; in others, it affects the lungs, joints, gastrointestinal system, and heart. The precise relationship between malignancy and DM has not been elucidated, but most experts agree that patients with DM have an increased risk of cancer.

Gottron papules are the most common cutaneous manifestation of DM. They are a palpable, symmetric skin eruption over the extensor surfaces of the metacarpophalangeal and interphalangeal joints of the hands and are pathognomonic for DM. Other skin findings include a heliotrope rash of the periorbital and upper eye area and a V- or shawl-shaped macular erythema over the chest and back. Hyperkeratosis of the palmar and lateral surfaces of the fingers is frequently present, referred to as mechanic’s hands. Less often, papulovesicular rashes, subcutaneous panniculitis, erosive lesions, or exfoliative erythroderma are seen.

The incidence of both adult and juvenile DM is 2 to 3 times greater in female than male patients, suggesting a pathophysiologic role for female sex hormones. In general, estrogens exert immunostimulatory effects, and androgens, immunosuppressive effects. Sex hormones have been shown to be involved in connective tissue disorders such as rheumatoid arthritis and lupus erythematosus and likely play a part in other autoimmune diseases including DM.

See also pages 65, 109, and 113

Many lines of evidence have also implicated tumor necrosis factor α (TNF-α) in the pathogenesis of DM. First, UV light is known to be a potential trigger of the skin eruption of DM, and in vitro studies have shown that UV-B light initiates release of TNF-α from human keratinocytes and fibroblasts. Second, Werth et al have reported an association of DM with the -308A TNF-α promoter polymorphism, which mediates a markedly increased TNF-α response to UV-B. Finally, a pathogenic role for TNF-α has been implicated in conditions clinically similar to DM such as juvenile DM and inflammatory myopa-
Case 1 was a 32-year-old white woman seen in 1993 with a mass in her left breast. She was found to have stage 1 breast carcinoma and was treated with a left partial mastectomy, irradiation, and chemotherapy. Four months later, she developed an erythematous, violaceous skin eruption on her face, arms, and thighs. A skin biopsy finding was consistent with DM, and the patient began treatment with hydroxychloroquine sulfate, which temporarily stabilized her eruption.

After 3 months, however, the rash deteriorated, and she began to experience dysphagia and weight loss. She was admitted to the hospital for further evaluation. Findings from another skin biopsy were again consistent with DM. Her erythrocyte sedimentation rate was elevated (105 mm/h), and lactate dehydrogenase and aspartate transaminase levels increased (to 401 and 178 U/L, respectively). Her creatine kinase levels at the time of admission are not known. Anti-ribonucleoprotein (anti-RNP) antibody findings were negative, and anti-Jo-1 and Mi-2 antibodies were not measured. Her chest radiogram was normal other than postoperative changes in the left chest wall. An esophagogram was normal.

The patient began treatment with oral prednisone at 30 mg/d, which was increased to a maximum of 60 mg/d and eventually tapered. The patient’s rash and dysphagia improved during therapy with prednisone, and the patient was discharged.

The patient also took twice-daily 10-mg doses of oral tamoxifen, a selective estrogen receptor modulator (SERM), as an adjuvant therapy from 1993 until 1997 to prevent recurrence of her breast cancer. During this time, her rash resolved, and she did not require therapy for her DM.

There were no signs of malignancy on regular physical examinations, blood work, or imaging. In 1997, however, shortly after her tamoxifen treatment was discontinued, she experienced an exacerbation of her DM skin eruption. She has since continued to manifest a heliotrope malar rash, erythema over her anterior superior chest and upper back, involvement of the extensor surface of the arms, and Gottron papules over the extensor surfaces of her hands, despite therapy with various immunosuppressants including prednisone, chloroquine, quinacrine hydrochloride, and methotrexate. The absence of evidence of a recurrent or new malignancy argues against a paraneoplastic process underlying her skin exacerbation. Antiestrogen therapy was not reimplemented in this patient, but it would be interesting to determine if subsequent exposure to antiestrogen medication would again mitigate her DM rash.

Case 2 was a 49-year-old white woman seen in 1998 for a pronounced erythematous rash following sun exposure. Her rash was prominent over the malar distribution, the upper extensor arms, and the dorsum of her hands including the knuckles (Gottron papules). She also had some periungual erythema and capillary changes in the nail bed. Laboratory findings, including evaluation of creatine phosphokinase and aldolase, were essentially normal. A skin biopsy was not performed as the clinical presentation was highly characteristic of amyopathic DM. The patient’s rash improved on a maximum oral hydroxychloroquine dose of 200 mg twice daily but did not remit completely.

The patient was evaluated for underlying malignancy, and findings from periodic screenings for gynecologic or breast cancer (including mammogram) were all negative. In 2003, she developed breast cancer, which was treated with a lumpectomy and radiation therapy. Adjuvant therapy with anastrozole, an aromatase inhibitor, was also started to prevent recurrence of the breast cancer. One month after initiation of anastrozole treatment, the patient’s DM rash subsided completely, and she was able to decrease her hydroxychloroquine dose for the first time since 1998. While the resolution of this patient’s eruption coincided closely with the start of anastrozole therapy, it is also possible that treatment of the underlying malignancy precipitated the improvement. It would be of interest to note whether her skin lesions would recur if therapy with anastrozole was stopped.

**COMMENT**

Tamoxifen, a SERM, is currently the most extensively used hormonal treatment for all stages of hormone-responsive breast cancer. It has also been approved for the prevention of breast cancer in high-risk women. Generally, SERMS exert antiestrogen effects on certain tissues (eg, breast) and paradoxical estrogen agonist effects on other tissues (eg, bone). The molecular mechanisms underlying these tissue-specific actions have not been fully elucidated. Unique physiologic effects, however, seem to involve distinctive SERM estrogen receptor conformations and binding of different adaptor proteins to either positively or negatively regulate target gene transcription.

In postmenopausal women with or without a history of breast cancer, tamoxifen augments spine and hip bone mineral density (BMD) more than 1% per year. In premenopausal women, however, tamoxifen is associated with a mean annual loss in spine BMD of 1.44%. Patients taking tamoxifen are at increased risk for venous thromboembolism, and approximately 1% of postmenopausal women taking tamoxifen for 5 years will have a thromboembolic event. Tamoxifen also increases the occurrence of localized endometrial cancer, benign uterine disease, and cataracts.

Aromatase inhibitors, such as anastrozole, constitute another class of hormonal treatment approved for adjuvant therapy in postmenopausal women with breast cancer. Anastrozole is a potent, selective, nonsteroidal inhibitor of aromatase and blocks the conversion of androgens to estrogen. Aromatase is expressed in ovarian, adipose, skin, muscle, bone, and brain cells. Recent phase 3 trials suggest that aromatase inhibitors may be superior to tamoxifen in the adjuvant setting, and they may replace tamoxifen as the adjuvant therapy of choice for postmenopausal women with breast cancer. Compared with patients taking tamoxifen, those taking anastrozole have a decreased risk of vascular and uterine adverse events but a slightly increased risk of fractures.

Antiestrogen drugs such as tamoxifen and other SERMs have been found to inhibit the production of cytokines and factors such as interleukin 10, TNF-α, and transforming growth factor β1.

Carruba et al showed that...
estrogen increases TNF-α synthesis and apoptosis in macrophage-like cells, while the combination of estrogen and tamoxifen completely abolishes induction of TNF-α. In addition, toremifene, another SERM, has been shown to reduce TNF-α secretion by monocytes. Estrogen, therefore, may have a proinflammatory effect, which is mediated through TNF-α production by immune or other cells and inhibited by certain antiestrogen medications.

Based on experimental evidence supporting a pathogenic role for TNF-α in DM, researchers have attempted to use anti-TNF-α therapy to treat cutaneous and muscular manifestations of DM: the successful use of infliximab fore, may have a proinflammatory effect, which is mediated through TNF-α. In addition, toremifene, another SERM, has been shown to reduce TNF-α secretion by monocytes. Estrogen, therefore, may have a proinflammatory effect, which is mediated through TNF-α. Estrogen, therefore, may have a proinflammatory effect, which is mediated through TNF-α. Estrogen, therefore, may have a proinflammatory effect, which is mediated through TNF-α.

Herein, we describe 2 patients with DM rashes that improved under treatment with antiestrogen medications. One of these patients experienced a relapse in her skin eruption when she stopped taking tamoxifen after 4 years of use. In addition, the use of tamoxifen in a 67-year-old man with DM and unilateral gynaecomastia secondary to a gonadotrophin-secreting oat-cell carcinoma of the lung has been reported. When he was treated with cytotoxic drugs and tamoxifen, his tumor showed only partial regression, but his gynaecomastia disappeared, and his DM went into remission.

One explanation for these observations is that ovarian or peripherally derived estrogens facilitate stimulation of pro-inflammatory cytokines such as TNF-α by immune cells, which circulate and interact within the skin. Alternatively, estrogens may induce proinflammatory cytokine production by skin cells themselves. These events may be blocked by antiestrogen medications. Most likely, the role of estrogens in the pathogenesis of DM involves the modulation of numerous immunologic pathways, but it is also possible that estrogens play a nonimmunologically mediated role in DM.

While the systematic assessment of antiestrogen drugs in the treatment of breast cancer has evolved considerably over the last 30 years, the ability of tamoxifen and other antiestrogen medications to modify rheumatologic and dermatologic disease remains to be investigated. The cases we have reported illustrate the potential for antiestrogen medications to modulate dermatologic diseases such as DM. Studies with larger groups of patients and longer observation periods are needed to better define the relationship between autoimmunity and hormonal status in DM as well as the risks and benefits associated with antiestrogen therapy in the long term. In addition, further elucidation of the biological pathways mediated by hormones in autoimmune disorders like DM could lead to novel therapies of benefit to specific subsets of patients with hormone-susceptible disease.

Accepted for Publication: September 21, 2005.
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Author Contributions: Study concept and design: Werth and Sereda. Acquisition of data: Werth and Sereda. Analysis and interpretation of data: Werth, Dany, and Sereda. Drafting of the manuscript: Sereda. Critical revision of the manuscript for important intellectual content: Werth. Study supervision: Werth.

Financial Disclosure: None.

Funding/Support: This article was funded in part by grants from the Lupus Research Institute, National Institutes of Health (1K24AR002207-01), and a Veterans Affairs Merit Review Grant (Dr Werth).

REFERENCES