Letter to the Editor

Dermatomyositis Illustrating the Gender Gap: A Retrospective Analysis of a Series

Dear *Cutis*®:

Dermatomyositis is an acquired multisystemic inflammatory disease mainly affecting the skin and skeletal muscles in adults and children. Although the exact etiology is unclear, pathogenesis involves T-cell activation by various triggers and immunopathogenic mechanisms. Studies on mice and humans indicate that females are more prone to developing autoimmune diseases such as the prototype models systemic lupus erythematosus and multiple sclerosis, and more than 75% of patients with autoimmune diseases, including dermatomyositis, are females, while males tend to develop systemic lupus erythematosus later in life or because of hormonal dysregulation.[1,2] This gender gap becomes even more prominent in females of childbearing potential. These striking gender differences have been attributed to the dimorphic effect of sex steroids on the development and function of the immune system in males and females.[1,2]

For the past several years, the gender perspective has gained popularity in an increasing number of medical areas as gender becomes one of the parameters used to account for differences in the pathogenesis, course, and outcomes of diseases. We undertook this retrospective analysis of 8 patients with adult-onset dermatomyositis to examine the gender distribution, clinical course, histologic features, serologic abnormalities, and possible association with internal malignancy or drug intake in this series. Discussions of the origins of gender differences in autoimmune diseases focus on dermatomyositis.

Methods

Data were collected from computerized files of 8 patients with dermatomyositis consecutively hospitalized in the dermatology department from January 1998 to September 2006. Age, gender, clinical parameters, histologic and immunologic features, outcome, and paraneoplastic background were recorded. The patients were classified according to the criteria for dermatomyositis described by Bohan and Peter[3]: typical dermatologic features including Gottron papules, heliotrope, and periungual involvement; the presence of symmetric muscle weakness of the limb girdle or anterior flexors of the neck; myositis on muscle biopsy; elevated muscle enzyme levels; and abnormal electromyogram.

Results

The 7 women and 1 man included in our study ranged in age from 48 to 78 years (mean age, 59 years). Three patients had definite dermatomyositis, 4 had probable dermatomyositis, and 1 patient did not meet the criteria and was diagnosed with amyopathic dermatomyositis. The Table summarizes the clinical data on the patients.

All patients presented with skin eruptions of a mean duration of 8 weeks, 6 patients had myalgia or muscle weakness, and 3 patients reported other accompanying symptoms such as arthralgia, dysphagia, and dyspnea. Concomitant internal malignancy was present in 3 women: 2 with advanced carcinoma of the breast and 1 with stage III carcinoma of the ovary.

Drug intake before the onset of the disease consisted of chemotherapy (paclitaxel, doxorubicin hydrochloride, carboplatin) in 3 patients, with a combined protocol in which one agent was paclitaxel in 2 patients and doxorubicin hydrochloride and carboplatin in 1 patient; levothyroxine sodium for hypothyroidism in 2 patients; alendronate sodium for prevention of osteoporosis in 3 patients; and hormone replacement therapy in one patient. One patient reported occupational exposure to epoxy resin in glue.

Physical examination of the skin revealed typical findings of dermatomyositis: 7 patients exhibited Gottron papules and heliotrope, 4 had periungual alterations, and 3 had poikiloderma.

Seven patients had elevated muscle enzyme levels. Extended serology for collagen disease was positive for antinuclear antibodies in titers greater than 1:80 in 5 patients in a speckled pattern on all tests. Other positive serologies encountered were antiribonucleoprotein and antihistone in one patient.

Lesional skin biopsy specimens demonstrated interface dermatitis of a vacuolar type in all patients. Direct immunofluorescence was positive for immunoreactants in the dermoepidermal junction only in 2 patients.

Clinical Data on Patients With Dermatomyositis (N=8)[a]

Parameter	Patients, n (%)
Gottron papules	7 (87.5)
Heliotrope	7 (87.5)
Periungual alterations	4 (50)
Poikiloderma	3 (37.5)
Muscle clinical involvement	6 (75)
Other clinical involvement (arthralgia, dysphagia, dyspnea)	3 (37.5)
Elevated muscle enzyme levels	7 (87.5)
Positive ANA titer (>1:80; speckled pattern)	5 (62.5)
Positive DIF for immunoreactants	2 (25)
Abnormal EMG	4 (66.7)[b]
Association with internal malignancy	3 (37.5)
Association with drug intake	4 (50)

Abbreviations: ANA, antinuclear antibody; DIF, direct immunofluorescence; EMG, electromyogram.
[a]Female to male ratio of 7 to 1; age range, 48–78 years (mean age, 59 years).
[b]Electromyograms were performed in 6 patients.

Electromyograms performed in 6 patients revealed myositis or myopathic changes in 4 patients. Muscle biopsy was performed in only one case that did not show characteristic inflammatory changes.

Seven patients were treated with oral corticosteroids—prednisone up to 60 mg/d with gradual tapering over several weeks. Patients were instructed to avoid sun exposure and use sunscreen. Four patients responded well to treatment, evidenced by partial to near complete clearance of skin lesions and subsidence of muscle involvement as determined by clinical examination and normal muscle enzyme levels.

On follow-up after an average of 24 months, 4 patients had died (2 from causes related to the primary internal malignancy and 1 from acute respiratory failure connected with dermatomyositis). One patient died without any relation to dermatomyositis or malignancy.

Comment

Gender differences in the incidence and course of diseases have long been recognized. The finding of female predominance in our series of patients with dermatomyositis is in agreement with the 3:1 to 12:1 ratios of females to males reported at all ages,[4-6] with the exception of one report of male predominance.[7] This gender gap was almost uniformly related to behavioral differences such as early consultation for cutaneous eruptions.

Female predominance among patients with dermatomyositis may be attributed primarily to the immunopathogenesis of the disease that makes females more susceptible to dermatomyositis and other autoimmune disorders. Females are more prone to developing autoimmune diseases such as the prototype models systemic lupus erythematosus and multiple sclerosis. Females generally are more immunologically reactive than males, mounting higher antibody levels and more potent responses to infectious agents. Sex steroids influence the development and function of the immune system differently in males and females, with a greater immune responsiveness to exogenous insults and autoimmunity in females.[8] The prevailing concept of gender dimorphism is that androgens are anti-inflammatory and depress both cellular and humoral immunity, while estrogens enhance it in a more complex way. Estrogens activate the immune system, ameliorate helper T cell type 1 responses, and induce or accelerate helper T cell type 2 responses. Autoimmune diseases are believed to result from activation of T cells and polyclonal activation of B cells that lead to exaggerated production of autoantibodies, in many cases targeting the skin. Based on studies performed on lesional skin from various autoimmune cutaneous disorders, including dermatomyositis,[9] it appears that the cells targeted for immunologic damage are epidermal basal keratinocytes.[1,2] Moreover, it is suggested that the pathomechanism involves an apoptotic pathway in the epidermis, evidenced by the specific distribution of different cellular proliferation markers such as Ki-67, p53, and bcl-2.[10]

A female predominance is expected in dermatomyositis as in other autoimmune disorders because female sex hormones are responsible in part for the specific immunologic background that favors cutaneous autoimmune manifestations. Exposure to sex hormones is mainly endogenous but could be the consequence of intake of exogenous hormones in the form of oral contraceptives or hormone replacement therapy, as one of our patients reported.

The internal malignancy rate of 37.5% (3/8) in our review is higher than the associated internal

malignancy rate of 14% (41/291) in a large review of the literature on adult dermatomyositis.[11] The fact that all of our patients with neoplasia were women with primary malignancies (eg, carcinoma of the breast, carcinoma of the ovary) also argues for the involvement of female sex hormones in the pathogenesis of paraneoplastic autoimmune skin disorders.

Interestingly, 3 of our patients underwent chemotherapy before the onset of their cutaneous eruptions; the agents were paclitaxel, doxorubicin hydrochloride, and carboplatin. Indeed, dermatomyositislike reactions have been associated with various drugs, most commonly chemotherapeutic agents, including hydroxyurea, tegafur-uracil, cyclophosphamide, and etoposide.[12,13] There is only one report of dermatomyositis in a patient treated with preoperative chemotherapy (paclitaxel and cisplatin) for ovarian carcinoma; this case exhibited regression with amelioration of the muscular manifestations of dermatomyositis but without parallel amelioration of the skin manifestations.[14] Nonchemotherapeutic agents include D-penicillamine and lipid-lowering drugs.[10]

Drug-induced dermatomyositis usually displays cutaneous lesions identical with true dermatomyositis. Muscular involvement is variable and the immunologic findings are scarce.[12] Although drug involvement is hard to establish, we consider paclitaxel, in addition to the paraneoplastic background, to be the cause of dermatomyositis in one of our patients, a supposition strengthened by the improvement of skin lesions upon withdrawal from the paclitaxel protocol.

Clinical cutaneous manifestations in our study, as in other series, confirm the relevance of Gottron papules and heliotrope, the most frequent lesions, as pathognomonic features in the diagnosis of dermatomyositis.

Associated muscle involvement and other complaints such as arthralgia, dysphagia, and dyspnea were reported by many of our patients and need to be addressed at admission because of their potential to escalate quickly, especially in the respiratory system.

Our finding of a high prevalence of a positive antinuclear antibody titer in a speckled pattern in most patients also is in agreement with reported data.[5] On the other hand, our series showed fewer cases of deposition of immunoreactants on examination with direct immunofluorescence than expected, probably because biopsies were performed in early lesions in which the immunologic process had not fully developed. Nevertheless, these findings argue that immunofluorescence microscopy has little value in the evaluation of cutaneous dermatomyositis or in distinguishing it from cutaneous lupus erythematosus.

In summary, we suggest that the finding of a female predominance among patients with dermatomyositis illustrates the gender gap in this disorder and is closely connected to the immunopathogenesis of the disease that makes females more susceptible to dermatomyositis and other autoimmune disorders. Based on our findings and the findings of others, we suggest an aggravating chemotherapeutic agent be investigated in cases of paraneoplastic dermatomyositis.

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The authors report no conflict of interest.

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