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Dermatologic Disorders in Patients with Thymoma

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We describe the cutaneous disorders in 172 patients with thymoma. Myasthenia gravis was the most common additional disease. Cutaneous disorders were found in 34 patients; 19 had skin disorders at the time of diagnosis of thymoma and 15 developed skin disorders after diagnosis of thymoma. Cutaneous fungal diseases were found in fewer than 10% of the patients (tinea pedis excluded). One patient with chronic mucocutaneous candidiasis was included in this group. Two patients with lichen planus, 2 with pemphigus, 2 with myositis, and 1 with lupus-like disease were also included in this study. Patients with skin disorders were no different than patients without these disorders with regard to thymoma histology, age at diagnosis, sex, or presence of myasthenia gravis. There were no associations between these variables and the patients who developed these skin disorders after diagnosis of thymoma. Thymectomy did not alter the clinical course with respect to cutaneous diseases. *Key words: Lichen planus; Mucocutaneous candidiasis; Myositis; Pemphigus.* (Received August 10, 1986.)

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Disorders of the skin found with tumors of the thymus gland have interested clinicians and stimulated attempts to explain these phenomena. The thymus plays a key role in the immunologic status of an individual and an association of disorders of the thymus with autoimmune diseases may occur. The autoimmune diseases most commonly associated with thymomas are myasthenia gravis, hypogammaglobulinemia, and pure red cell aplasia. Other types of immune-related diseases, not involving production of autoantibodies but also reported with thymoma, are mucocutaneous candidiasis and disseminated dermatophytosis.

Our interest in dermatologic manifestations in patients with thymoma was prompted by two recent patients evaluated at the Mayo Clinic who had pemphigus and myasthenia gravis in addition to thymomas. A review of patients with thymoma was undertaken with regard to other dermatologic conditions. We hoped to gain some idea about the frequency, patterns of onset of these skin conditions, and response to treatment. In addition, characteristics separating those patients with skin disorders from the others were sought.

MATERIALS AND METHODS

Clinical material was obtained through a review of all patient histories that had a final diagnosis of thymoma from 1963 through 1983. A histologic diagnosis of thymoma made at the Mayo Clinic was required for inclusion in the study. Histologically, these tumors were classified as lymphocytic type, epithelial type, spindle-cell type, or mixed types of the previous three. For those patients still alive, follow-up data were obtained through Jan. 1, 1983, via a patient visit to the clinic or a letter sent to the patient with a questionnaire regarding his or her general health, presence of any skin disorders or other disease, and summary of treatments. We included all skin conditions noted during examinations at the Mayo Clinic or those discovered by follow-up letter.

RESULTS

Of the 172 patients who met the study criteria, 88 were men and 84 were women (mean age at time of thymoma diagnosis, 53 years). Thirty-four of these patients had skin findings: 16

men and 18 women (mean age at time of thymoma diagnosis, 55 years). The skin disorder was present in 19 of 34 patients at the time of diagnosis of thymoma; 15 patients developed the skin disorder later. The histologic types of thymoma are summarized in Table I.

Cutaneous findings and number of patients were: cutaneous fungal infection, 14—tinea corporis in 6, onychomycosis in 5, and tinea pedis in 3; oral yeast, 5; chronic mucocutaneous candidiasis, 1; pemphigus, 2; lichen planus, 2; herpes zoster, 5; basal cell carcinoma, 2; malignant melanoma, 1; psoriasis, 1; multiple truncal seborrheic keratoses, 3; chronic aphthous ulcers, 2; and related autoimmune disorders—polymyositis in 1, sclerodermatomyositis (Sjögren's syndrome) in 1, and polyarthritis and cyclic edema (lupus-like disease) in 1. The patient with Sjögren's syndrome also had Raynaud's phenomenon and gastrointestinal changes consistent with scleroderma.

Systemic autoimmune-type diseases found in the whole group and the number of patients were: myasthenia gravis, 68; hypogammaglobulinemia, 8; red cell aplasia, 2; Graves' disease, 2; and 1 each of polymyositis, inflammatory bowel disease, pernicious anemia, rheumatoid arthritis, lupus erythematosus-like disease, sclerodermatomyositis, and Raynaud's disease.

Systemic autoimmune diseases in the group with cutaneous findings included myasthenia gravis in 10 patients, hypogammaglobulinemia in 4, and Graves' disease, rheumatoid arthritis, and chronic ulcerative colitis in 1 each.

Pemphigus

Both of the patients with pemphigus were male and had myasthenia gravis—in one it was severe enough to cause respiratory compromise and in the other it was asymptomatic but documented by single-fiber electromyography (EMG) and acetylcholine receptor antibody assay (Table II).

Table I. *Histologic type of thymoma and dermatologic disease*

	Dermatologic disease, no. of patients	
	Yes	No
Lymphocytic	10	31
Mixed lymphoepithelial	15	55
Epithelial	7	39
Spindle	1	10
Other	1	3
Total	34	138

Table II. *Dermatologic disorders and thymoma in patients with pemphigus*

Sex	Age at diagnosis (yr)	Thymoma		Skin disorders	Other disorders
		Type	Extent		
M	54	Lympho-epithelial	Circum-scribed	P. erythematosus, dermatophytosis	Myasthenia gravis + ANA
M	42	Lympho-epithelial	Regional extension	P. vulgaris, h. simplex, candida	Myasthenia gravis

Fungal disease

Seventeen patients had a fungal or yeast disease. Of the 5 patients who had oral yeast infections, one of these was the patient mentioned above with pemphigus vulgaris. Two had dermatophytosis, 1 had lichen planus, and 1 had mucocutaneous candidiasis with skin, nail, and esophageal candida, keratitis, and chronic ulcerative colitis. This latter patient has been reported previously (1).

Lichen planus

In patients who had lichen planus, the oral cavity was involved and one also had lesions on the back. The latter patient had the diagnosis of lichen planus made coincidentally with diagnosis of thymoma. The thymoma was lymphocytic and thought to be circumscribed. However, this patient died $1\,^1/_2$ years later, secondary to nonthymic problems. The former patient is a male who had lichen planus 4 years prior to diagnosis of thymoma (spindle-cell type, circumscribed, and totally resected). The patient also has recurrent fungal infections of the groin, fingernails, and toenails and he has hypogammaglobulinemia. He is alive 12 years after resection of the thymoma.

Statistical analysis

Analyses were conducted to determine if there were associations between skin disorders and the variables of thymoma histologic type, age, sex, and myasthenia gravis.

Myasthenia gravis was the only "associated" disease occurring with any evaluable frequency (n=68). The 172 patients were divided into two groups: the 19 patients with existing skin disorders and the 153 patients without existing skin disorders. The χ^2 test (two-tailed) was used to test for associations between each of the groups and the above variables. No significant associations were found (all p values were >0.20).

DISCUSSION

Although reviews of thymoma patients have been published, cutaneous disease descriptions were apparently ignored or given little attention. Our current series does not differ from the reviews already published (2, 3) in terms of age, sex, tumor type, and percentage of patients with myasthenia gravis or other autoimmune diseases. Several cutaneous diseases were documented in our series of thymoma patients. This is the largest review of this type done specifically in search of cutaneous disease. Isolated case reports have been relied upon in the past for data regarding these cutaneous diseases in thymoma patients. This study places these conditions in a framework with regard to thymoma. The finding of pemphigus along with myasthenia gravis or thymoma or both has been reported in more than 30 patients (4–13). In patients with thymomas, myasthenia gravis, and pemphigus, the erythematosus variant is somewhat more common than vulgaris. A total of 24 patients have been reported to have thymoma and pemphigus. Not all patients with myasthenia gravis and pemphigus had thymomas. There is a male predominance of thymoma patients with pemphigus and we add two more patients to this total of 24, 19 of whom are male. Pemphigus erythematosus is the variant most commonly seen in this group. Both histologic thymoma types in our patients were lymphoepithelial, as were at least two of the previously reported cases. One of our patients had onset of the pemphigus after diagnosis of thymoma and the other was before diagnosis of thymoma. However, time of diagnosis is not synonymous with onset of tumor and we suspect that the thymoma preceded the pemphigus in both patients. This was also usually the case in previous reports of these two conditions. At least six previous reports of these conditions specified that the thymomas were malignant. One of our patients had a malignant thymoma. Removal of the nonmalig-

nant thymoma has had no effect on the course of our patient with pemphigus with regard to the blistering eruption and the tinea corporis.

Autoantibodies present in the patient with pemphigus erythematosus included acetylcholine receptor antibodies, antistriational antibodies, antinucelar antibodies (ANA), and antinative DNA. ANA and antinative DNA were not present in the patient with pemphigus vulgaris. The titer of acetylcholine receptor antibodies tended to decrease as the patient with pemphigus vulgaris improved clinically, but the patient with pemphigus erythematosus never had muscle weakness. The latter patient has numerous autoantibodies, but relatively mild blistering and no clinical evidence of systemic lupus. Pemphigus and the acetylcholine receptor antibodies do not seem to be linked because titers vary independently of one another. An association has been postulated but not prove with regard to pemphigus and thymoma.

Fungal disease

Seventeen of our 172 patients had some type of fungal disease; 4 had toe-web involvement alone. Because these patients were not specifically examined for cutaneous fungus, this total is probably conservative. Five of our patients had documented oral yeast. One of these 5 patients fits well into the chronic mucocutaneous candidiasis syndrome (CMCC). This case was reported earlier (1). Two other patients with oral yeast infections and 1 patient with CMCC also had dermatophytosis. Shama & Kirkpatrick (14) reported that 12 of 60 patients with CMCC also had dermatophyte infections.

Kirkpatrick & Windhorst (15) described 27 patients who had CMCC (type V) and thymoma. None of the patients was susceptible to candida infections during infancy or childhood; treatment-resistant candida of the nails, skin, and mucous membranes develop en in adulthood. These characteristics are also true of our patient. Eleven of 27 patients had malignant thymomas, as did our patient with CMCC.

CMCC is a distinctive syndrome and can be considered to be associated with thymoma. It is not clear whether onychomycosis or dermatophytosis of the body can be considered to be a thymoma-associated disease. Of all patients with tinea corporis or onychomycosis, only a small number will have thymoma.

Lichen planus

Lichen planus with thymoma has been reported. The following diseases were also seen in this group of patients: ulcerative colitis, myasthenia gravis, alopecia areata, vitiligo, and hypogammaglobulinemia (16–18). Of 3 previous patients with thymoma and lichen planus, all had erosive painful oral lesions and lesions on the body. Two the these 3 also had oral candida and the other developed dermatophytosis of the feet and groin. Thymoma preceded development of lichen planus in 2 of these 3 patients. Both patients who had lichen planus in our series also had oral lesions. Both of our patients also had fungal disease and 1 had hypogammaglobulinemia. The similarities among these 5 patients are striking. Lichen planus is thought to be an immune-mediated disease for several reasons, including the findings of immune reactants at the basement membrane zone on direct immuofluorescence, predominance of helper T cells in the infiltrate, and its similarity to graft-versus-host disease. A cause-and-effect relationship between lichen planus and thymoma has not been documented.

Connective tissue disease

Myositis has been reported in association with thymoma (19–23). Neither of our 2 patients had dermatologic changes consistent with dermatomyositis. One of these patients with myositis also had keratoconjunctivitis sicca, Raynaud's disease, and small bowel changes

consistent with scleroderma. This patient's clinical course was not apparently altered by thymectomy, similar to a case reported by Alarcón-Segovia & Zavala-Mejía (24).

Systemic lupus erythematosus has been reported in association with thymoma and with metastatic squamous cell carcinoma of the skin (25, 26). Perhaps lack of suppressor T-cell activity is the common thread that joins these autoimmune disorders with thymoma. Suppressor cell activity can be restored in patients with lupus by incubation with thymosin or cultured thymic epithelium (27). Whether thymoma represents a reaction to a generalized immune disorder or predisposes to development of these disorders is not clear. Except for myasthenia gravis, thymectomy does not clearly have a beneficial effect in the treatment of these disorders.

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