Acta Dermatovener (Stockholm) 52: 393–397, 1972

PEMPHIGUS AND THYMOMA

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Abstract. Pemphigus vulgaris and a benign thymoma occurred in a 62-year-old man who had no clinical signs of myasthenia gravis. Direct and indirect immunofluorescence was positive for intercellular epithelial antibodies. Indirect immunofluorescence was positive for antinuclear antibodies and for antibodies against striated muscle and negative for antibodies against thymic tissue.

Thymic abnormalities have been reported with myasthenia gravis, and with other diseases that are characterized by deficiencies in cellular and humoral immunologic reactivity. Approximately 30% of patients with thymoma have myasthenia gravis (11). Fifteen percent of patients with myasthenia gravis have thymomas and 60% have some type of thymitis (9). Cases have been reported of myasthenia gravis or thymoma associated with myositis, myocarditis, dermatomyositis, rheumatoid arthritis, scleroderma, candidiasis, pemphigus and systemic lupus erythematosus (1, 2, 3, 11, 14, 16, 22, 24, 27). Kough & Barnes (15) reported a patient with benign cystic thymoma, erythroid aplasia, and a bullous skin eruption who had positive L.E. cell tests.

We here describe a case of thymoma and pemphigus vulgaris, but with no evidence of myasthenia gravis.

REPORT OF A CASE

A 62-year-old black man was first hospitalized at the Bronx V.A. Hospital on November 10, 1969 for a recurrent bullous eruption of 6 months' duration on the trunk and extremities and mucous membranes of the mouth. Biopsy of an intact blister revealed an acantholytic, intra-epidermal lesion suggestive of pemphigus foliaceus. The condition gradually improved upon application of topical steroids. The patient was next seen at that hospital on May 5, 1970 for hoarseness and difficulty in swallowing of 4 months' duration. Flaccid bullae and excoriations were present on the skin and erosions on the oral mucosa. Laryngoscopy showed the left vocal cord to be paralysed. Conventional X-ray examination and tomograms of the chest showed an anterior mediastinal mass. Angiography of the aortic arch revealed no disturbance in the location of the adjacent pedicles of the vessels by the retrosternal mass. No anomalies were found in an upper G.I. series and a thyroid scan. There was leukopenia (3 500/mm^3) and thrombocytopenia (110 000/mm^3). A bone marrow examination showed normal findings. Direct and indirect Coombs tests were negative. Results of other routine laboratory examination and liver function tests were normal.

On July 21, 1970 an exploratory mediastinostomy was performed and a benign thymoma measuring 10×5 cm was removed from the superior anterior mediastinum. Clinical tests for myasthenia gravis and electromyographic examination of the first dorsal interosseus and abductor digiti quinti muscles were performed and found normal. There was a normal response to stimulation of the orbicularis oculi muscle. The skin condition remained under control upon application of topical steroids.

The patient was first seen by our group when he was admitted to the Manhattan Veterans' Hospital on June 29, 1971 because of an exacerbation of the bullous eruption on the face, trunk, extremities and oral mucosa. There was erythema and excoriation of the penis and mild erythema and crusting of the scrotum. There were a few small well-circumscribed areas of erythema and scaling on the dorsa of the feet and maceration between the toes. The toenails showed dystrophic changes. Mycologic examination was positive for T. rubrum in scales from the dorsa of the feet and for Candida albicans in specimens from the skin of the penis and scrotum. No clinical evidence of neuromuscular disease was found.

Biopsy of an intact bulla from the anterior chest revealed suprabasilar acantholysis consistent with pemphigus vulgaris. The patient's serum by indirect immunofluorescence was positive for intercellular epithelial antibodies at a 1 : 160 dilution. It was positive for antinuclear antibodies (diffuse pattern) at a 1 : 160 dilution and against striated muscle at a 1 : 10 dilution. The serum was negative for antibodies against thymic tissue. Direct immunofluorescence of a bulla was positive for intercellular antibodies but negative on a specimen from a clinically unaffected area of skin.

Table I. *Findings in cases of pemphigus associated with myasthenia gravis and/or thymoma*

		Myasthenia gravis	Thymoma	Pemphigus	Pemphigus auto-antibodies	Striated muscle auto-antibodies	Thymic tissue auto-antibodies	Anti-nuclear antibodies
1	Kough & Barnes, 1964	Not present	Present	Present	Not done	Not done	Not done	Positive
2	Peck et al., 1968	Present	Present	Present	Positive	Positive	Positive	[b]
3		Present	Not present	Present	Positive	Positive	Positive	[b]
4		Present	Not present	Present	Positive	Negative	Negative	[b]
5		Present[a]	Not present	Present[a]	Negative	Negative	Negative	[b]
6	Beutner et al., 1968	Present	Present	Present	Positive	Positive	Not done	Positive
7	Jablonska et al., 1970	Present	Not present	Present	Positive	Positive	Not done	Positive
8	Stillman & Baer, 1971	Not present	Present	Present	Positive	Positive	Negative	Positive
	Totals	6/8	4/8	8/8	6/7	5/7	2/5	4/4[c]

[a] Disease in state of remission.
[b] ANA for individual patients not reported. However 7/24 of their patients with pemphigus had positive ANA.
[c] Does not include Peck et al.

Tests for delayed hypersensitivity revealed strongly positive reactions to trichophytin, streptokinase/streptodornase, histoplasmin, coccidioidin, and mumps antigen, and a slightly positive reaction to oidiomycin. Intermediate strength PPD caused blistering in addition to erythema and induration. Sensitization to 2,4-dinitrochlorobenzene was successfully attempted.

Upon routine laboratory study, the only abnormal findings were a mild leukopenia (3 800/mm^3) and thrombocytopenia (110 000/mm^3). The erythrocyte sedimentation rate was within normal limits. Indirect and direct Coombs tests were negative. Tests for serum auto-antibodies against white blood cells and platelets were negative. LE preparation was negative.

Quantitation of the serum immunoglobulins by means of radial immunodiffusion revealed the following: IgG 1 700 mg% (normal 570–1 900), IgA 300 mg% (normal 60–330), and IgM 110 mg% (normal 45–145). Total serum iron was normal but iron binding capacity was low. Serum electrophoresis indicated a low total gamma globulin level.

The patient's skin condition gradually responded to alternate day treatment with prednisone 250 mg and ACTH 40 units i.m.

COMMENT

We were able to demonstrate the presence of auto-antibodies for intercellular epithelial sites, nuclei and for striated muscle, but no other immunologic anomalies. In particular, the cell-mediated immune responses to common microbial antigens were not only not depressed but were unusually strong in our patient.

The discovery of the localization of auto-antibodies around epithelial cells in pemphigus vulgaris and certain other forms of pemphigus has led to speculation that these antibodies may play a role in the pathogenesis of these diseases. Beutner et al. (4) and Sams and Jordon (26) have offered evidence against a direct involvement of the antibody in the production of the bullous lesions of pemphigus. However, Grob & Inderbitzin (12, 13) reported experimental production of anti-epithelial auto-antibodies in rabbits by means of immunization with homologous antigen, derived from epithelium of rabbit esophagus. Acantholysis occurred at the site of the auto-antibodies in the epithelium. This suggests the possibility that acantholysis can be triggered by an immunologic mechanism.

Peck et al. (24) reported 4 patients who had concurrent myasthenia gravis and pemphigus vulgaris. One of the patients had, in addition, a malignant thymoma. Three showed a high in-

direct immunofluorescent titer to areas of intercellular stratified epithelium. Two of the latter also had auto-antibodies against striated muscle. Beutner et al. (3) and Jablonska et al. (14) each reported a patient with myasthenia gravis and pemphigus erythematosus who had antibodies to skeletal muscle, to the intercellular areas of stratified squamous epithelium and to nuclei, as revealed by indirect immunofluorescence. In addition, the patient reported by Beutner et al. (3) had a malignant thymoma (Table 1). It is noteworthy that neither in the patient reported by Kough & Barnes (15) nor in our patient did the bullous skin eruption clear after thymectomy. Whittingham & Mackay (31) detected "pemphigus" intercellular antibodies on indirect immunofluorescence in 1 of 40 patients with SLE and 2 of 26 patients with myasthenia gravis.

Beutner et al. (3) note that the striated muscle antibody titers do not appear to parallel the disease activity of myasthenia gravis as closely as the fluctuations in the intercellular antibodies parallel the clinical changes of pemphigus.

The demonstration of auto-antibodies to striated muscle and thymic epithelial cells in sera of patients with myasthenia gravis and/or thymomas supports the theory that these diseases are caused by some disturbance of the immunopoietic system. Strauss et al. (29) demonstrated an antibody which reacts with the striations of skeletal muscle and also with myoid cells in the thymic medulla. The serum factor which stained the striations of skeletal muscle was identified as a component of the gamma globulin fraction (5).

Myasthenia gravis and pemphigus seem to occur simultaneously much more frequently than would be expected by chance. Burnet (8) attaches importance to the findings in the thymus in myasthenia gravis and postulates that similar disturbances may occur in cases of other autoimmune diseases.

The overall function of the thymus in immunity appears to be that of regulating maturation of stem cells in lymphocyte production, so as to maintain the normal pool of immunocompetent cells (30). Burnet (8) regards the thymus as the chief "first level" immunological organ in which the lymphoid cells arise which proliferate to produce functionally active descendant or collateral cells in the "second level" immunological organs (spleen, lymph nodes and bone marrow). He suggests that the thymus is the site of initiation of natural immune tolerance which is established in embryonal life, presumably by inactivation of cells with the capacity for self-reactivity. He hypothesizes that cells in the thymus that could react with auto-antigens (the "forbidden clones") are normally inhibited or destroyed instead of being permitted to proliferate. If, instead, the cells are stimulated to proliferate by the antigen present in the thymus, then this initiates an autoimmune type of response. Thus the normal thymus plays an important role in preventing the emergence of these "forbidden clones". In postulating the role of the thymus in maintaining self-tolerance, Goldstein & Mackay (11) added to this theory by suggesting that stem cells are induced to immunologic competence and "tested" for self-reactivity against a "library" of auto-antigens within the thymus. Self-reactive cells would die within the thymus and only cells which did not react with auto-antigens would survive and emigrate to join the circulating pool of immunologically competent lymphocytes, able to produce the characteristic cellular and humoral responses. They (17) used the concept of a tolerogenic function of the thymus to account for the presence in the thymus of structures such as muscle (myoid cells) and squamous epithelium (Hassall's corpuscles); tolerance induction to these major components of the body might require their representation as such in the thymus. Possibly the developing thymus contains most of the accessible auto-antigens of the body. If the occurrence in post-natal life of thymic disease, thymitis, or thymoma, so changed the thymic milieu that auto-antigens which are present in the thymus (i.e. cell nuclei, myoid cells, and squamous epithelium) had an immunologic rather than a tolerogenic effect, the result could well be the formation of auto-antibodies to those constituents. This might explain the associations between thymic disease, particularly thymoma, and autoimmune diseases such as systemic lupus erythematosus, myasthenia gravis and bullous skin diseases (31).

That the cell-mediated immune-responses of the patient were not depressed may be explained by the fact that thymectomy in the adult, unlike thymectomy in the newborn, has no immediate effect on immunological capability. Presumably this is the result of an adequate existing pool of

long-lived, immunocompetent cells. Only when the pool becomes depleted do immunological defects become evident (21). Thymectomies performed in rabbits (18) and adult mice (20) have little effect upon immunocompetence. The long-lived, thymus-dependent lymphocytes ("T cells") constitute a substantial portion of all lymphoid cells in the recirculating pool. In comparison, the bursa-dependent lymphocyte ("B cell"), which is responsible for humoral immunity, is short-lived (10).

It is of interest that our patient demonstrated auto-antibodies by immunofluorescence against striated muscle as well as against intercellular substances in skin. The presence of "pemphigus" antibodies has been demonstrated in serum over 1 year prior to onset of clinical manifestations of pemphigus (31). Our patient thus far has no clinical or electromyographic signs of myasthenia gravis. In the light of the presence of antibodies against skeletal muscle one can anticipate the possibility of his developing myasthenia gravis in the future. If this does evolve, it could be interpreted as additional evidence favoring the autoimmune etiology of these diseases.

It is noteworthy that while pemphigus and the associated intercellular antibodies have been reported concomitant with thymoma and autoimmune diseases such as SLE and myasthenia gravis, pemphigoid and the basement membrane antibodies have, to our knowledge, never been reported in association with these diseases. On the other hand pemphigoid, and presumably also the associated basement membrane antibodies, are occasionally associated with internal malignancy, so as to make it necessary to consider a possible causal relationship (6, 7, 19, 23, 25, 28). This observation points in the direction of two separate groups of autoantigens or of two very different mechanisms inducing formation of auto-antibodies in these diseases.

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Received January 31, 1972

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