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Coexistence of Myasthenia Gravis and Pemphigus Foliaceus

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Myasthenia gravis and pemphigus are both considered to have an autoimmune basis. Although immunological and clinical studies have been performed on large numbers of patients with myasthenia gravis, the coexistence of myasthenia gravis and pemphigus foliaceus has rarely been described. We recently have the opportunity to study a 33-year-old female patient having both of these autoimmune diseases confirmed by various diagnostic methods. This rare coexistence of myasthenia gravis and pemphigus foliaceus has not been previously documented in Korea.

Key Words : *Myasthenia gravis, Pemphigus foliaceus, Autoimmunity*

INTRODUCTION

Myasthenia gravis (MG) is an autoimmune disease, resulting from the production of antibodies against the acetylcholine receptors of the neuromuscular junction (Patrick and Lindstrom, 1973 ; Lindstrom et al., 1988 ; Levin and Richman, 1989).

MG is frequently associated with morphological abnormalities of the thymus. The most common finding is thymic follicular hyperplasia, seen in about 65 to 75% of myasthenic patients and thymoma is found in approximately 15%. Up to 15% of patients with MG have thyroid disease, approximately 4% have rheumatoid arthritis. Dermatologic disorders such as pemphigus and vitiligo are rarely associated with MG (Keesy, 1991).

At the present time, the number of cases of coexisting MG and pemphigus is small. In Korea, there has been no reported case of coexistence of MG and pemphigus. So, we present a case of coexistent MG and pemphigus foliaceus with some review of the literature.

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CASE REPORT

A 33-year-old woman with a 4-year history of refractory pemphigus was admitted. Fourteen years previously, she had noted weakness in both legs, usually occurring in the late afternoon. She had difficulty in climbing steps and complained of intermittent blurred vision. Her symptoms were aggravated by postpartum. But she had no previous history of treatment. In 1990, a widespread pruritic eruption on the whole body except the lips developed. According to medical records of Asan medical center, the skin biopsy specimem from lesional trunk documented intraepidermal bulla with acantholysis. At that time, she was treated with prednisolone (60mg/day). But she discontinued the drug because her symptoms failed to subside. Three months later, she treated herself with dapsone. Because of deterioration of her clinical status, she was admitted to our hospital in May, 1994. The patient showed a widespread, non-photosensitive skin eruption over her face, chest and back (Fig. 1). She was treated under the impression of pemphigus foliaceus with prednisolone

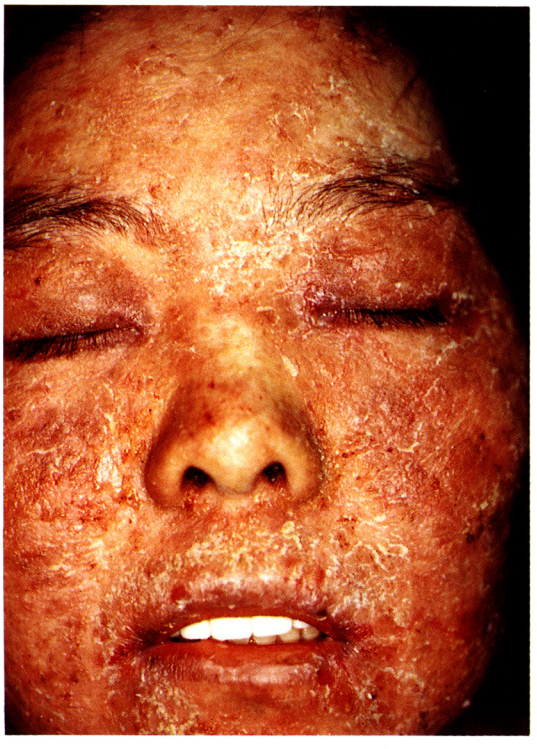

Fig. 1. Scaly erythematous skin lesion of face.

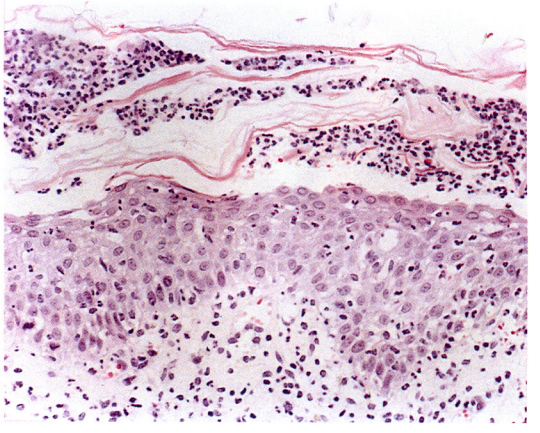

Fig. 2. Biopsy specimen revealing a subcorneal epidermal acantholysis (Hematoxylin-Eosin stain)

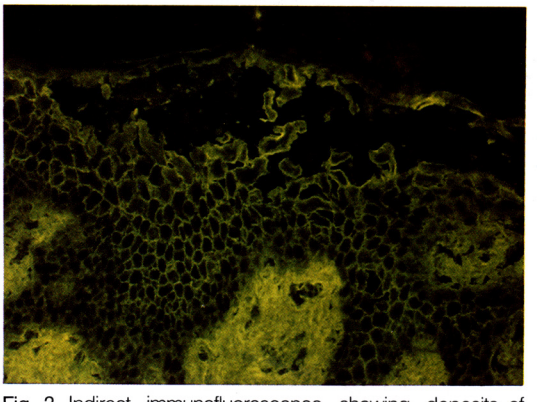

Fig. 3. Indirect immunofluorescence showing deposits of autoantibody at the intercellular substance of epidermal keratinocytes.

(60mg/day) for 7 days. On the 8th hospital day, the patient developed sudden respiratory failure and general weakness. On neurological examination, she had a bilateral ptosis, decreased deglutition, decreased muscle power in both upper and lower extremities, and respiratory muscle. A strong response to edrophonium chloride (Tensilon) was observed. Tentative diagnosis was myasthenic crisis with pemphigus. Electrophysiologic studies indicated the lesion was the neuromuscular junction and myasthenic reaction was noted in the Jolly test. The results of routine blood, urine, thyroid, liver and electrolytes studies were normal. There was no radiographic evidence of thymoma by mediastinal CAT scan. A hematoxylin-and-eosin stain of a biopsy specimen from lesional skin on the trunk showed intraepidermal blistering (Fig. 2). Direct immunofluorescence showed intercellular IgG deposit in a pattern that outlined epidermal keratinocytes. Indirect immunofluorescence showed that the patient had circulating antibodies that bind specifically to the intercellular spaces of stratified squamous epithelium (Fig. 3). The pemphigus antibody titer was determined and positive intercelluar staining was observed to the titer of 160. Serum complement C3 was 49.2 mg/dl and C4, 31.5 mg/dl respectively. It was proved that this patient had circulating antibodies directed against the pemphigus foliaceus antigen (DAKO, Co) by immunoblotting study (Fig. 4). The peripheral T-lymphocytes versus B-lymphocytes was 64 : 26 and CD4 (T helper cell) versus CD8 (T suppressor cell) was 75 : 25 measured by flow cytometry (VENDER, USA). Additional laboratory investigation revealing the positive acetylcholine receptor antibody in the patient's serum (140 nmol/L) by radioimmunoassay method (COSMIC Co, USA) confirmed the diagnosis of MG.

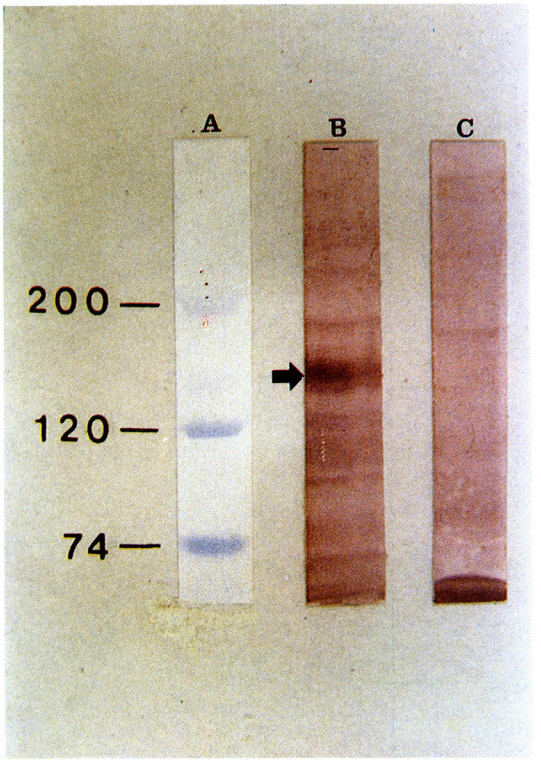

Fig. 4. Immunoblot analysis showed binding of serum autoantibodies (IgG) on the epidermal protein of 160 kD [A, molecular markers (kD); B, patient's autoantibody (IgG) reconizing 160 kD antigen (arrow); C, normal control].

Cutaneous lesion and myasthenic weakness were much improved after the patient received Mestinon, prednisolone and Imuran.

DISCUSSION

It is widely accepted that neuromuscular abnormalities in myasthenia gravis are due to autoantibody mediated process. The supporting evidence is as follows : 1) Serum antibodies to acetylcholine receptor are present in 80 to 90 % of patients with MG (Lindstrom et al, 1976 ; Vincent and Newsom-Davis , 1985). 2) The presence of IgG at neuromuscular junctions has been described by electron microscopic examination in the specimen of MG patient (Engel et al., 1979). 3) Repeated injections of IgG from patients with myasthenia gravis into mice reproduced the characteristc features of the disease (Toyka et al., 1977). 4) Immunization of a variety of animal species from frog to primates to acetylcholine receptor clearly demonstrated that the immune response directed against acetylcholine receptor was capable of reproducing myasthenia gravis (Patrick and Lindstrom, 1973). 5) A reduction of antibody levels ameliorated MG (Dau et al., 1979 ; Hertel et al., 1979).

In addition to MG, pemphigus is also accepted as an autoimmune disease (Beutner et al., 1965 ; Chorzelski et al., 1966). Pemphigus has circulating antibodies that bind specifically to the intercellular spaces of stratified squamous epithelia (Beutner and Jordon , 1964 ; Peck et al., 1968). The intercellular antibodies may play a pathogenic role in the disease. The earliest events in acantholysis that are responsible for the intraepidermal blistering in pemphigus are believed to occur in the intercellular cement space (Hashimoto and Lever, 1970). Most patients with pemphigus demonstrated IgG autoantibodies directed against an antigen located on the surface of keratinocytes. Our patient's serum yielded a 160-kD epidermal protein band in the epidermal extracts, which is known as a pemphigus foliaceus antigen (Fig. 4). The major histologic feature is acantholysis and several mechanisms have been proposed to explain the pathogenesis of acantholysis. It was postulated that the pemphigus antibodies induced acantholysis through local stimulation of the plasminogen--plasmin system and the pemphigus antibodies fixed complement and altered cell membrane integrity to produce acantholysis (Korman, 1988). This suggests the possibility that acantholysis can be triggered by an immunologic mechanism.

The spontaneous coexistence of pemphigus and myasthenia gravis is well documented (Maize et al., 1975 ; Troy et al., 1981 ; Garlepp et al., 1983 ; Kaplan and Callen, 1983). According to previous reports, MG preceded pemphigus and most of the subtype showing this association was pemphigus vulgaris except in the case reported by Maize, which was pemphigus foliaceus as in this case. The clinical course was variable, although the most common evolution was the initial development of myasthenia gravis, followed by the appearence of pemphigus. The onset of pemphigus was usually heralded by some initiating factors of the precipitants, such as thymectomy or thymic irradiation, sun exposure, drugs, infection or contact dermatitis (Cruz et al., 1987). In our case, pemphigus foliaceus began 10 years after MG and no possible precipitant was detected.

Regarding the origin of the autoimmune response

in the two diseases, the thymus has been implicated as a possible site of origin. The thymus contains myoid cells and Hassall's corpuscles, structures similar in appearance to muscle and epidermis, respectively. Myoid cells bear surface acetylcholine receptors and Hassall's corpuscles are remnants of the epithelial portion of the primordial thymus (Kao and Drachman, 1977). Cross-reactivity between skeletal muscle antibodies in myasthenia gravis and myoid cells in the thymus has been demonstrated (Garlepp et al., 1983).

Because of their strategic location within the thymus, surrounded by antigen presenting cells and helper T-cell, the acetylcholine-receptor-bearing myoid cells may be particularly vulnerable to immune attack (Kirchner et al., 1988). The autoantibodies could arise secondarily to a primary insult of the thymus such as viral infection (thymiditis), and molecular mimicry (Schwimmbeck et al., 1989). Some alteration of the myoid cells or lymphocytes, or a breach of immune regulation, may interfere with tolerance and lead to an autoimmune response. Also, cross-reactivity between bacteria and acetylcholine receptor has been reported (Stefansson et al., 1985).

In addition to the antigenicity of myoid cells, it has been suggested that alteration of thymic Hassall's corpuscles antigenicity in the setting of thymic hyperplasia or thymoma might be responsible for the generation of pathogenic keratinocyte antibodies (Maize et al, 1975).

An alternative explanation of failure of the T-cell suppression permitting autoantibody production has also been postulated. This T-cell defect could result in a failure to recognize itself from nonself and become manifest as T-cell autoaggressive activity against skeletal muscle as well as autoantibody formation against muscle, nucleoproteins, DNA, and epidermal intercellular cement. (Maize et al., 1975 ; Kaplan and Callen, 1983). The failure of T-cell suppression represented as the changing ratio between T-helper cell (CD4) and T-suppressor cell (CD8) and a result of an increment in the CD4 to CD8 ratio in peripheral blood. In our case, the ratio was 3.0(CD4/CD8=75/25). In this paper, we report a rare case of coexistence of myasthenia gravis and pemphigus foliaceus. This combination have occurred as an autoimmune basis and probably due to some defect of the thymus.

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