Association of Myasthenia Gravis with Pemphigus Vulgaris, Candida albicans Infection, Polymyositis and Myocarditis

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INTRODUCTION

There have been occasional reports of the association of myasthenia gravis with polymyositis, myocarditis, pemphigus, or Candida albicans infection. These associations are of interest not only with regard to diagnosis and management, but also because of possible common etiology and pathophysiology in these disorders. The present report describes a patient with myasthenia gravis, who also had pemphigus vulgaris and Candida albicans infection, and subsequently developed polymyositis and myocarditis.

CASE REPORT

A 52-year-old man developed diplopia, followed in 3 weeks by ptosis, more pronounced on the right, slight difficulty in talking, chewing, and swallowing, with nasal regurgitation, and mild weakness of the muscles of the neck and limbs. Family and past history were not contributory. There was bilateral ptosis, and the maximum width of the palpebral fissure on upward gaze was 8 mm on the right and 8.5 mm on the left, which became 5 mm and 6.5 mm, respectively, after maintaining upward gaze for 1 min. The orbiculares oculi were moderately weak, and the neck flexors and arm elevators were slightly weak. Eye movements were normal, and there was no other detectable weakness or wasting of muscle. Ptosis disappeared temporarily following intravenous injection of edrophonium chloride. Radiologic examination of the chest was normal. The serum globulin bound to cross-striations of skeletal muscle at a titer of 1:810 (normal, less than 1:90) and reacted with isolated human skeletal muscle membrane by the complement fixation method at a titer of 1.63 units (normal, 0–94 units). Antinuclear antibody and rheumatoid factor were negative. A diagnosis of mild, generalized myasthenia gravis was made. The symptoms were controlled by the oral administration of 90 mg pyridostigmine bromide every 3 hr during the daytime.

The course was uneventful until 10 months after the onset of the disease, when the patient developed aggravation of ptosis, abdominal cramps, and diarrhea, following pyridostigmine administration. Reduction in the dose of pyridostigmine alleviated ptosis and abdominal complaints, but caused marked weakness of the shoulder girdle muscles and of swallowing, voice, and breathing, indicating different responsiveness.

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of various muscle groups to pyridostigmine. The patient was therefore hospitalized (first admission) 19 months after onset of the disease. During this hospitalization, electromyography revealed a decrement of the amplitude of repetitively evoked action potentials of the orbicularis oculi, but not of the abductor digiti minimi. Maximum motor and sensory nerve conduction velocity and motor unit potentials were normal. A biopsy of the right palmaris longus revealed lymphorrhages. Muscle fibers had a normal diameter, ranging from 35 to 70 µm and average of 45 µm in frozen-sections, with no sign of degeneration. Motor end-plates were normal, without elongation or fragmentation. Motor nerve terminals also appeared normal, with no excessive branching. Other laboratory examinations were normal, including serum creatine phosphokinase (0 unit; normal, 0-12 units), glutamic oxalacetic transaminase (9 units; normal, 3-40 units), lactic dehydrogenase (260 units; normal, 50-300 units), and protein-bound iodine (6.4 µg/100 ml). Lupus erythematosus cells were not present. The electrocardiogram was normal. The patient was discharged from the hospital 1 month later with improved muscle strength on 45 mg pyridostigmine bromide and 0.5 g potassium chloride orally every 3 hr during the daytime and 180 mg pyridostigmine bromide “time-span” at bedtime. Ephedrine sulfate, 25 mg orally 3 times a day, was added later.

Six months later, the patient felt well and discontinued medication, only to resume in 2 months because of a recurrence of ptosis and weakness of the neck flexors. At the same time (28 months after the onset of myasthenia gravis), he developed red, tearing eyes, running nose, painful lesions in the tongue and throat, and reddish-purple skin rash. Because of the pain, he did not eat properly and lost about 20 pounds. When he was hospitalized (second admission) 3 months after the onset of the muco-cutaneous complications, there was bilateral conjunctivitis, encrustation of the lips, and hyperemia, white plaques and painful ulcerations on the tongue, buccal mucosa and pharynx. There were raised, reddish-purple papulobullous eruptions on the skin of the waist, volar surface of the wrist, and penis. Muscle weakness was limited to the levator palpebrae, orbicularis oculi, and arm elevators. Hematologic studies were normal including white cell count of 5700/mm$^3$, with 1% eosinophils. Serum protein was 6.4 g/100 ml with 60% albumin, 5% $\alpha$-1-globulin, 11% $\alpha$-2 globulin, 14% $\beta$-globulin and 10% $\gamma$-globulin. Repeated cultures grew Candida albicans from the pharynx and tongue. Urine cultures were negative for bacteria. Serum Candida agglutinin titer was elevated to 1:320 (normal, 1:1-1:60). Serologic tests for rheumatoid factor, antinuclear factor, syphilis, histoplasmosis, blastomycosis, and coccidiodomycosis were negative. The muco-cutaneous lesions were thought to be pemphigus vulgaris, with secondary oral infection of Candida albicans. The serum contained a globulin which bound, by the immunofluorescence method, with the “intercellular” substance of the stratified squamous epithelium at serum dilutions up to 1:80 (Fig. 1), a finding compatible with pemphigus. Sera which had been obtained and stored frozen before the onset of the muco-cutaneous symptoms, were negative for “intercellular” binding globulin. The patient was given triamcinolone applied topically to the skin lesions, and prednisone and nystatin orally. The skin lesions disappeared in about 2 weeks, but the oral lesions improved only slightly at the time of discharge from the hospital 19 days later. Replacement

![Fig. 1. Binding of the serum globulin with intercellular substance of the stratified squamous epithelial cells (upper left) and with cross striations of skeletal muscle (lower right). Rat esophagus. Immunofluorescence method. x 764.](image-url)
of pyridostigmine bromide by pyridostigmine chloride had no effect, ruling out bromism as a cause. The conjunctival and nasal secretions were temporarily alleviated by the oral administration of 50 mg of benadryl or topical application of phenylephrine hydrochloride, and disappeared after 2 months.

The patient was hospitalized for the third time, 35 months after the onset of myasthenia gravis, for 8 days for readjustment of medication because he became weaker, with difficulty in holding up his head and mild dyspnea. Meanwhile the oral lesions were unchanged and he lost 35 pounds. *Candida albicans* was again cultured from the oral lesions. After discharge he received further treatment elsewhere with corticosteroids by oral administration and by injection into the oral lesions, and 2 courses of oral methotrexate, 2.5 mg daily for 2 weeks, without change in the oral lesions or muscle strength.

Following an episode of sore throat, he developed profound, generalized weakness, with ptosis difficulty in holding up his head, speaking, and breathing. Five days later and 44 months after onset of myasthenia gravis, he was hospitalized (fourth admission). The temperature was 98.6°F, blood pressure 100/60 mm.

### TABLE I

DURATION AND AMPLITUDE OF MOTOR UNIT POTENTIALS*

<table>
<thead>
<tr>
<th>Number</th>
<th>Duration (msec)</th>
<th>Amplitude (µV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deltoid</td>
<td>7</td>
<td>2.43 ± 0.20</td>
</tr>
<tr>
<td>Biceps brachii</td>
<td>9</td>
<td>3.67 ± 0.44</td>
</tr>
<tr>
<td>Extensor digitorum communis</td>
<td>10</td>
<td>2.60 ± 0.27</td>
</tr>
<tr>
<td>First dorsal interosseus</td>
<td>8</td>
<td>3.63 ± 0.46</td>
</tr>
<tr>
<td>Quadriceps femoris</td>
<td>6</td>
<td>5.83 ± 0.65</td>
</tr>
<tr>
<td>Tibialis anterior</td>
<td>10</td>
<td>3.90 ± 0.61</td>
</tr>
<tr>
<td>Gastrocnemius</td>
<td>13</td>
<td>5.15 ± 0.66</td>
</tr>
</tbody>
</table>

* Mean ± S.E. Obtained with concentric needle electrode.

![Electrocardiogram during the last hospital admission. Pulse rate, 96/min.](image)
Hg and pulse 120/min. He was orthopneic and dyspneic, with labored respirations of limited excursion at 32/min. His face was slightly cushingoid. White plaques and ulcerations were still present on the tongue and buccal mucosa. A few coarse rhonchi were heard in the chest and slight pretibial edema was present. There was moderate ptosis bilaterally, marked weakness of the neck muscles and of the elevators of the arms, and moderate weakness of the limb muscles. Following intravenous administration of 2 mg edro-

Fig. 3. Muscle fiber necrosis and lymphoid cell infiltration in the diaphragm (A), intercostal muscle (B), and left ventricle (C), HE. × 113.
phonium chloride, his muscle strength and respiratory excursion improved. An intramuscular injection of 0.5 mg neostigmine methylsulfate produced further improvement in strength, particularly of the flexors of the neck. However, there was still moderate generalized muscle weakness, particularly of the elevators of the arms. Hematologic studies were normal, except for an erythrocyte sedimentation rate of 24–32 mm/hr. Serum total protein ranged from 5.4–6.3 g, with 3.2–3.8 g albumin, per 100 ml. Serum electrolytes were normal. The urine did not contain hemoglobin or myoglobin. The following serum enzymes were elevated for the first time: creatine phosphokinase, 118–143 units; aldolase, 119 units (normal, 3–8 units); lactic dehydrogenase, 300–775 units; and glutamic oxalacetic transaminase 70–236 units. The muscle striation-binding globulin was increased to a titer of 1:2430; and the “intercellular” binding globulin was unchanged at a titer of 1:810. Repeated cultures from the mouth and pharynx were negative for Candida albicans, and serum Candida agglutinin and precipitin tests were normal. Electrophysiologically, the myasthenic reaction was again positive in the orbiculares oculi, and, on this examination, motor unit potentials were of short duration, low amplitude (Table I), and occasionally polyphasic, with an interference pattern composed of a greater number of spikes than normal. Electrocardiograms during this admission showed tachycardia, regular sinus rhythm, Q waves in leads V2 and V3, flattened T waves in leads I and aVL, suggesting anteroseptal myocardial damage (Fig. 2). Biopsy of the buccal mucosa revealed edematous epithelium, particularly in the stratum spinosum, acantholysis, and mild to moderate infiltration of round cells and eosinophils, a finding compatible with pemphigus vulgaris. A biopsy of the right deltoid muscle revealed greater variation of muscle fiber diameter ranging from 20–150 μm, foci of muscle fiber necrosis with phagocytic infiltration, slight increase in connective tissue, and interstitial and perivascular lymphoid cell infiltration, changes compatible with polymyositis. The skin overlying the deltoid muscle was normal. The patient was treated for myasthenia gravis with 0.5 mg neostigmine methylsulfate intramuscularly every 2 hr, and 15 mequiv. potassium chloride orally 3 times a day. Dyspnea, orthopnea, and basal pulmonary rales became more marked and were attributed mainly to left heart failure, which was treated with digitalization and diuretics from the third hospital day. The polymyositis was treated with 20 mg methylprednisolone intramuscularly 3 times daily from the fifth day. The patient’s condition did not improve and he was found dead in bed on the fifteenth hospital day.

Post-mortem examination revealed skeletal muscle fiber necrosis, interstitial and perivascular lymphoid cell infiltration, including lymphorrhages, thickening of blood vessels, and increased connective tissue. These changes were extensive in the diaphragm (Fig. 3A), deltoid, and intercostal muscles (Fig. 3B); moderate in the levator palpebrae and rectus bulbi superior muscles; and focal in the obliquus bulbi superior and rectus abdominus muscles. The thymus weighed 4.5 g and was normal microscopically. The heart weighed 420 g. The coronary arteries were patent, with a calcified plaque at the orifice of the right coronary artery. There was necrosis of cardiac muscle fibers with vacuolar changes, accompanied by lymphoid cell infiltration. These changes were diffuse and pronounced in the left ventricle (Fig. 3C) and focal in other parts of the myocardium. There were atheromatous patches in the aorta, congestions in the liver, spleen, kidney, and lung, and mucous secretions in the bronchi. The thyroid weighed 20 g, was symmetric and firm, and had interstitial lymphoid cell infiltration (Fig. 4). The adrenal glands were normal.
DISCUSSION

Association of myasthenia gravis with polymyositis

There have been 58 reported patients, including the present patient, who had both myasthenia gravis and polymyositis (References, Part A): 20 patients had both myasthenia gravis and polymyositis; 13 patients, including the present patient who had myasthenia gravis and later developed polymyositis; 4 patients who had myasthenia gravis, and in whom polymyositis was found at post-mortem study; and 21 patients with polymyositis who had some feature of myasthenia gravis. The 58 patients included 20 men and 32 women (39%:61%). The age of onset of myasthenia gravis or polymyositis ranged from 14 to 75 years (median 41.5 years). Nineteen patients (33%: 95% confidence limits, 21–47%) had a thymoma. Post-mortem examination was described in 13 patients, and 7 had myocarditis, while 6 of these 7 also had a thymoma. Nineteen patients died after 54 days–10 years (median 14 months), and 34 patients were alive after 4 months–33 years (median 4.5 years).

In the 13 myasthenic patients who later developed polymyositis, including the present patient, the onset of myasthenia gravis was between the ages of 24 and 55 years with a median of 40 years; and polymyositis developed 1 to 30 years later with a median of 5 years. Three of these patients had a thymoma, and 1 patient, described in this report, had myocarditis. Five patients had both ptosis and diplopia, 2 had ptosis but without diplopia, 1 patient did not have ptosis or diplopia, and eye manifestations were not described in 5 patients. Muscle strength was improved by administration of anticholinesterase drugs in 8 of 8 patients. Electromyographic studies were compatible with myasthenia gravis in 5 of 5 patients, and with polymyositis in 7 of 7 patients. Muscle enzymes in the serum were elevated in 2 of 6 patients, and the erythrocyte sedimentation rate (ESR) was elevated above 20 mm in 1 hr in 2 of 6 patients.

Patients reported to have polymyositis with some features of myasthenia gravis differed from the patients of the other groups. The male to female ratio was 8:7 (53%:47%), compared with 12:35 (32%:68%) in the other groups. Response of muscle strength to anticholinesterase compounds was less uniform: improvement was definite in 5 patients, equivocal or partial in 13 patients, and absent in 2 patients, compared with definite improvement in 20 of 20 patients in the other groups ($P<0.001$). Electrophysiologic evidence of myasthenia gravis was found in only 2 of 9 patients compared with 11 of 12 patients in the other groups ($P<0.01$). On the other hand, the incidence of signs of polymyositis was not different significantly between these 2 groups: a myopathic electromyogram was present in 7 of 8 patients compared with 14 of 14 patients in the other groups, the serum enzymes were elevated in 3 of 5 patients compared with 3 of 8 patients in the other groups, and the ESR was over 20 mm in 1 hr in 6 of 10 patients compared with 4 of 10 patients in the other groups.

Of the 58 patients reported to have both myasthenia gravis and polymyositis, 35 were treated with corticosteroids and 19 with corticotropin. Muscle strength improved in most patients, but in a few (Bonduelle, Bouygues and Coulon 1955), including the patient of the present report, there was a decrease in muscle strength during administration of these drugs. It is likely that the exacerbation of the myasthenic component of the illness was responsible for the decrease in muscle strength, since, during ad-
ministration of these compounds, muscle strength usually improves in polymyositis, but often decreases in myasthenia gravis (Namba, Brunner, Shapiro and Grob 1971; Brunner, Namba and Grob 1972). Therefore, while corticosteroids and corticotropin are useful in the management of polymyositis and myasthenia gravis, one must be alert to the possible exacerbation of myasthenia gravis during the administration of these compounds.

Among primary myopathies, autoimmune processes have been studied most extensively in myasthenia gravis. The occurrence of thymoma (29% of patients, Grob 1958) and thymic hyperplasia (48%, Grob 1958), have been considered a reflection of immunologic abnormalities. The sera of myasthenic patients contain globulins which react with various cell components: in our studies, a globulin which bound with crossstriations of skeletal muscle was present in 43% of 242 patients, antinuclear globulin in 16% of 234 patients, and rheumatoid factor in 11% of 185 patients. The transfer of circulating lymphocytes of myasthenic patients produced severe "runt disease" in mice (Namba, Arimori and Grob 1969a) and myositis accompanied by morphological alterations of motor end-plates in rats (Namba, Arimori and Grob 1969b). Being one of the hypersensitivity diseases, polymyositis is also thought to have an autoimmune mechanism, and the serum and lymphocytes of such patients have had immunologic reactivities (Currie, Saunders, Knowles and Brown 1971). In our experience striation-binding globulin was positive in 18% of 43 patients with polymyositis, antinuclear globulin in 15% of 39 patients, and rheumatoid factor in 21% of 39 patients. It may therefore be assumed that myasthenia gravis and polymyositis are associated with altered immune mechanisms, although no common denominator has been found with regard to the etiology of these diseases.

Muscle wasting has been observed in 6% (4-10, 20 of 325 patients, Osserman 1958) to 22% (16-30%, 37 of 169 patients, Uono, Tanabe and Nakao 1970) of myasthenic patients. In our experience the wasting is generally diffuse and occurs in patients with severe muscle weakness for many years, but the wasting may be localized, as for example in the tongue, and may occur in patients with a duration of disease of less than a year. In some myasthenic patients, microscopic findings in muscle resemble the changes in polymyositis, with marked atrophy and degeneration of muscle fibres and extensive interstitial and perivascular cell infiltration. There are probably various causes for muscle wasting in myasthenia gravis, ranging from disuse atrophy to clear-cut myopathic changes, including a condition identical with polymyositis.

Association of myasthenia gravis or polymyositis with myocardial lesions

In a series of consecutive post-mortem examinations, microscopic myocardial lesions were found in 16 of 31 myasthenic patients (52%, 33-70%), including muscle fiber necrosis in 12 patients, lymphorrhages in 3 patients, and both lymphorrhages and mild muscle fiber necrosis in 1 (Mendelow and Genkins 1954; Genkins, Mendelow, Sobel and Osserman 1961). Of the 16 patients with cardiac lesions, 9 had a thymoma and 3 thymic hyperplasia, in contrast to only 1 patient each with thymoma and with thymic hyperplasia in the 15 patients without cardiac lesions, a statistically significant difference ($P < 0.03$). In another series of studies on 26 myasthenic patients,
extensive myocarditis was found in 2 patients, focal myocarditis in 1, and lymphorrhages in 3 (Rowland, Hoefer, Aranow and Merrit 1956). The serum of some patients with myasthenia gravis reacts immunologically with myocardium (Beutner, Witebsky, Ricken and Adler 1962; Namba and Grob 1966), but the significance of this reaction is not known. In spite of the incidence of microscopic myocardial lesions, clinical myocardial failure is rare in myasthenic patients, and the cause of death is usually attributed to respiratory failure. It is not known whether cardiac lesions develop only at the terminal stage of the illness and are the cause of sudden death which occurs in some patients.

In polymyositis, cardiac abnormalities are often present clinically, including electrocardiographic changes and arrhythmias, but microscopic lesions in the myocardium have been described in only 29 patients, including the subject of the present report (Giordano and Haymond 1944; Mendelow and Genkins 1954; Rowland 1955; Genkins et al. 1961; Rowland, Aranow and Hoefer 1961; Klein and Lennartz 1966; Burke, Medline and Katz 1969; Kinney and Maher 1940; O’Leary and Waisman 1940; Waller, Shapiro and Paltauf 1957; Walton and Adams 1958; Langston, Wagman and Dickenham 1959; Barnard, Rankin and Robertson 1960; Bignami and Calcara 1962; D’Agostino Avella and Maddaluno 1962; Rundle and Sparks 1963; Schmid 1965; McGuire and Smith 1967; Hill and Barrows 1968; Lynch 1971; Schaumburg, Nielsen and Yurchak 1971; Trylor, Templeton and Henderson 1970). Giant-cell reaction was present in the myocardium in 9 of these patients, and also in skeletal muscle in 7 of the 9 patients. Thymoma was found in all the 9 patients with giant-cell myocarditis, and in 1 additional patient with giant-cell reaction in skeletal muscle alone, but in only 1 of the remaining 19 patients without giant-cell reaction, a statistically significant difference \((P < 0.0001)\). Of the 29 patients with polymyositis associated with myocardial lesions, 7 patients, including the present patient, also had myasthenia gravis, and 5 of the 7 patients had giant-cell myocarditis.

**Association of myasthenia gravis with pemphigus vulgaris**

Myasthenia gravis and pemphigus vulgaris have been described in 9 patients, including the present patient and 2 with pemphigus erythematosus (association of pemphigus vulgaris and systemic lupus erythematosus: Beutner, Chorzelski, Hale and Hausmanowa-Petrusewicz 1968; Chorzelski, Jablonska and Blaszczyk 1968; Peck, Osserman, Weiner, Lefkovits and Osserman 1968; Peck and Osserman 1969; Jablonska, Chorzelski and Lebioda 1970; Ridley 1970). There was no sex predominance. Pemphigus developed 1–15 years after the onset of myasthenia gravis.

A serum immunoglobulin G of some patients binds with the substance between the cells of the stratified squamous epithelium, particularly at the stratum malpighii (Beutner, Chorzelski and Jordan 1970). This “intercellular” binding occurred in the serum of 88 % (83–92 %, 243 of 276 patients) of patients with pemphigus, including pemphigus vulgaris, pemphigus foliaceus, pemphigus erythematosus, pemphigus vegetans, and Brazilian pemphigus foliaceus, but was negative in the serum of 2935 patients with other diseases (Beutner et al. 1970), including patients with myasthenia gravis (Beutner 1969), and polymyositis (Kay and Tuffanelli 1969). However, recent reports described positive “intercellular” binding in other diseases, including 2 (7 %,
1–23 %) of 29 patients with myasthenia gravis (Whittingham and Mackay 1971), and some patients with polymyositis and lupus erythematosus (Anderson, Newcomer, Landau and Rosenthal 1970).

Of the 9 patients with both myasthenia gravis and pemphigus, both “intercellular” binding and muscle-striation-binding globulins were positive in 4 patients, 2 of whom had a thymoma; “intercellular” binding globulin was positive and muscle-striation-binding globulin was negative in 3 patients; and both globulins were negative in a patient whose pemphigus and myasthenia were in remission. Antinuclear factor was positive in the serum of 3 patients, 2 of whom had pemphigus erythematosus, and was negative in the present patient. Serologic studies were not described in a patient who died of membranous colitis (Ridley 1970).

Association of myasthenia gravis with Candida albicans infection

The association of myasthenia gravis with Candida albicans infection has been described in 3 patients: a man developed both myasthenia gravis and polymyositis 12 years after the onset of cutaneous and oral candidiasis and 3 weeks after thymectomy (Ehrenreich and Allen 1958; Green and Booth 1958; Rowland and Schotland 1965), in a woman generalized myasthenia gravis occurred 2 years after the onset of cutaneous candidiasis and 16.5 months after thymectomy (Schoch 1971); and generalized candidiasis developed in a man during a myasthenic crisis several years after the onset of myasthenia gravis and Candida albicans was cultured from inflammatory foci in skeletal muscle (Jellinger and Bankl 1971). Another patient with cutaneous candidiasis for a year developed radiologic evidence of thymoma and weakness of limb muscles, which resembled myasthenia gravis clinically and was accompanied by lymphorrhages in the calf muscle (Montes, Carter, Moreland and Ceballos 1968). Candida albicans has often been cultured from the tracheostomy site in our myasthenic patients. Candida infection occurs frequently and has been thought to play an etiologic role in familial benign chronic pemphigus, an acantholytic vesico-bullous disease transmitted by an autosomal dominant mode (Bruns, Reed, Swatek and Omieczynski 1967). Oral candidiasis in the present patient appeared to be a secondary infection of the lesions of pemphigus vulgaris, but may be related to a possible immuno-deficient state in myasthenia gravis and to treatment with corticosteroids.

SUMMARY

A 52-year-old man developed generalized myasthenia gravis, with pronounced oculobulbar muscle weakness. At the age of 54, he developed pemphigus vulgaris, manifested by papulo-bullous eruptions in the skin and oral mucosa, and by the presence of serum globulin which bound to intercellular substance of the stratified squamous epithelium. Candida albicans was repeatedly cultured from the oral lesions. At the age of 56, the patient developed severe weakness of trunk and limb muscles, and elevation in the serum of enzymes originating from muscle. The electromyogram was compatible with both myasthenia gravis and polymyositis, and the muscle biopsy with polymyositis. The electrocardiogram indicated myocardial damage. The patient died suddenly. Post-mortem examination revealed degenerative changes in
skeletal and cardiac muscle, with interstitial and perivascular round cell infiltration.
round cell infiltration of the thyroid, and a normal thymus. The patient demonstrated
the association of myasthenia gravis with polymyositis (58 reported patients) with
pemphigus vulgaris (9 reported patients), with Candida albicans infection. and with
lesions in the myocardium.

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