Thymoma with Pemphigus Foliaceus

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Abstract

A 75-year-old Japanese woman was referred to us because of an anterior mediastinal mass. Crusts and shallow erosions developed 10 months earlier on her upper chest, back, and scalp. Pemphigus foliaceus was diagnosed based on histological examination of skin biopsy specimens and positivity for serum anti-desmoglein 1 antibody by enzyme-linked immunosorbent assay. Neurological examination and electromyography ruled out myasthenia gravis. Total thymectomy was performed, and the postoperative pathology studies showed mixed lymphoepithelial thymoma. One year after the resection, the eruption and alopecia improved and the serum anti-desmoglein 1 antibody titer decreased, suggesting a beneficial effect of thymectomy on thymoma-related pemphigus.

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Key words: thymectomy, anti-desmoglein 1 antibody

Introduction

Although as many as 40% of thymoma patients have parathymic syndromes, including myasthenia gravis (MG) and other autoimmune disorders, cutaneous manifestations are rare (1). Pemphigus is an immunologically mediated skin disease characterized by epidermal blisters that may occur in association with thymic or nonthymic neoplasms (2, 3).

Since some patients with dermatological complaints consult an internist first, it is important to recognize skin disorders as possible sequelae of thymoma, the most common primary neoplasm in the mediastinum (1). We report a case of thymoma accompanied by pemphigus foliaceus (PF), a relatively rare form of pemphigus.

Case Report

A 75-year-old Japanese woman was referred to us in May

1998 for evaluation of an anterior mediastinal tumor detected on a routine chest radiograph taken after a 3-year interval. The previous chest radiograph, in June 1995, showed no abnormal shadows, suggesting that the abnormal finding had developed during the past 3 years. The patient had a 10-year history of noninsulin-dependent diabetes mellitus appropriately managed with oral hypoglycemic agents. The patient had first noticed crusts and shallow erosions on her upper chest, neck, back, and scalp, and alopecia in July 1997, and she had received steroid ointment but with no improvement. On admission, the results of the general examination were normal, except for alopecia and mild erosions on the scalp and trunk (Figs. 1, 2). The chest radiograph showed a well-defined, round anterior mediastinal mass, about 3 cm in diameter (Fig. 3). Computed tomography demonstrated a low-density anterior mediastinal mass without calcification, located adjacent to the right atrium, that was slightly enhanced by contrast medium (Fig. 4, top). T1-weighted magnetic resonance imaging showed that the mass had the same intensity as soft tissue and was encapsulated (Fig. 4, bottom). Bronchoscopy demonstrated no endobronchial lesions. CT of other body sites, and ⁶⁷Ga and bone scintigraphy showed no significant abnormalities. An electrocardiogram and echocardiogram were within normal limits. Peripheral blood counts and blood cell morphology were normal. Serum chemistry studies were normal except for modest elevation of hemoglobin A1c. Anti-acetyl choline receptor antibody was positive (6.6 nmol/l) (Table 1), but MG was ruled out because of the normal electromyogram and neurological examination. Skin biopsy specimens from the scalp and back showed acantholytic blisters that had formed in the superficial layers of epidermis (Fig. 5), a finding that was consistent with PF. Indirect immunofluorescence showed a positive reaction against intercellular substance (ICS) in the epidermis. Direct immunofluorescence examination clearly demonstrated deposits of C3 and immunoglobulin (Ig) G against ICS of the epidermis. The index value by antigen-specific enzyme-linked immunosorbent assay (ELISA) of serum anti-desmoglein (Dsg) 1 antibody was 167.9 and that of serum anti-Dsg 3 was 9.1, confirming the diagnosis of PF (4, 5). Total thymectomy was performed in May 1998. Mixed lymphoepithelial thymoma was diagnosed

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Figure 1. Crusted erythema and erosions on the trunk.

Figure 3. Chest radiograph on admission showing a mediastinal mass.

Figure 2. Crusted erythema on the scalp with severe hair loss.

Figure 4. A well-defined mass in the anterior mediastinum demonstrated by computed tomogram (top) and magnetic resonance imaging (bottom).

Table 1. Laboratory Findings on Admission

ESR	28 mm/h	TP	7.0 g/dl	ANA	×40 (DIF)
FOB	(-)	TB	0.2 g/dl	anti-AchR Ab	6.6 nmol/l
Urinalysis	normal	AST	14 IU/l	anti-desmoglein 1 Ab	167.9
		ALT	10 IU/l	anti-desmoglein 3 Ab	9.1
WBC	7,300/mm ³	LDH	135 IU/l	anti-DNA Ab	(-)
driff.	normal	γGTP	19 IU/l	anti-Sm Ab	(-)
RBC	409×10 ⁴ /mm ³	CK	34 IU/l	anti-SS A Ab	(-)
Hct	37.0%	BUN	10.5 mg/dl	anti-SS B Ab	(-)
Hb	12.7 mg/dl	Cr	0.5 mg/dl	CYFRA	<0.3 ng/ml
Plt	28.9×10 ⁴ /mm ³	Na	138 mEq/l	Pro-GRP	<8.0 ng/ml
Ret	1.0%	K	4.4 mEq/l	HCG	<0.04 ng/ml
		Cl	102 mEq/l	IgG	1,452 mg/dl
PT	84%	TC	154 mg/dl	IgA	174 mg/dl
APTT	30.2 sec	FPG	125 mg/dl	IgM	156 mg/dl
FNG	332 mg/dl	CRP	0.1 mg/dl		
		HbA1c	7.0%

Figure 5. Skin biopsy showing blisters and acantholytic cells in the superficial layers of the epidermis (HE stain, ×100).

based on the histological findings in the resected specimens (Fig. 6). The thymoma was considered to be at the clinical stage I because it was encapsulated and had no evidence of invasion to the adjacent organs (6). The patient was discharged in June 1998. The cutaneous lesions showed significant improvement, and the index value of serum anti-Dsg 1 antibody fell to 110.1 in May 1999, suggesting that resection of the thymoma had had a beneficial effect on the pemphigus. The anti-acetyl choline receptor antibody titer also decreased to 3.0 nmol/l at that time.

Discussion

Thymoma is the most common primary mediastinal neoplasm and is known to give rise to autoimmune disorders, including MG, pure red cell aplasia, and acquired hypogammaglobulinemia (1). MG is the most frequent of these parathymic

Figure 6. Lymphocytes and spindle epithelial cells were comparably observed in the resected specimen, resulting in a diagnosis of mixed lymphoepithelial thymoma (HE stain, ×400).

syndromes. Skin diseases are considered rare complications of thymoma, although blistering diseases, lichen planus, and cutaneous fungal infections have been reported to sporadically occur in association with thymoma (7). Pemphigus is a blistering skin disease first described by Wichmann in 1791 and now classified into two major subtypes, pemphigus vulgaris (PV) and PF (8). PF is characterized by the superficial distribution of acantholysis in the epidermis and is generally less severe than PV, which involves suprabasal layers of the epidermis (9). Although tests for circulating IgG autoantibodies against keratinocyte cell surface antigens are usually positive in PF and PV, the autoantigens of the antibodies differ (9). In PF, the autoantibodies are directed against Dsg 1, a 160-kDa desmosomal cadherin (10), whereas, in PV, the autoantibodies are against Dsg 3, a 130-kDa desmosomal cadherin (11). In the present case, deposits of C3 and IgG against ICS in the superficial layers of the epidermis demonstrated by direct immunofluorescence microscopy and detection of circulating anti-Dsg 1 antibody by ELISA confirmed the diagnosis of PF (4, 5).

Younus and Ahmed reviewed the 18 cases of thymic neoplasia with pemphigus described in the English literature up to 1990 (12). Only three were in females, and their average age was 51 years old. Of the 16 cases in which the time course was described, pemphigus preceded the thymic neoplasia in 5, thymic neoplasia preceded the pemphigus in 10, and both disorders developed simultaneously in 1. The subtype of pemphigus was PV in 8 and PF in 10, eight of which were diagnosed as pemphigus erythematosus (PE), a localized variant of PF. Twelve patients had benign neoplasms, and only 2 were reported to have malignant thymoma. Eleven cases of thymoma with pemphigus, including the present case, have been reported in Japan in the past 10 years (Table 2) (13–22). Mean patient age was 57 years old, and 9 patients were female, suggesting a much higher incidence of thymoma in Japanese female pemphigus patients. The subtype of pemphigus associated with thy-

moma in the Japanese population did not significantly differ from the subtypes in the cases reviewed by Younus and Ahmed (12), and involved 6 cases of PV and 5 of PF, including 3 cases of PE. The percentage of PE among thymoma-related pemphigus patients seems higher than that among general pemphigus patients, judging from the data of the Japanese national surveillance of pemphigus, which reported that PE accounted for 15% of Japanese pemphigus patients (23). Three patients were reported to have clinically significant MG. Thymoma preceded or occurred simultaneously with pemphigus in most of the cases over intervals up to 20 years. In the present case, the dermatological manifestations occurred 10 months prior to the diagnosis of thymoma. Since small thymic tumor could not be definitively ruled out even though a chest radiograph 3 years before the development of PF was nearly normal, we speculate that the thymoma in the present case preceded or developed simultaneously with the pemphigus.

Although the coexistence of thymoma and pemphigus was recognized in 1964 (24), it is not understood precisely why thymic neoplasms are associated with pemphigus. Callen thought that the immunological analogy between epithelial antigen in thymic tissues and epidermal antigen in skin played an important role in the relationship between them (25), while Imamura et al reported that serum from 3 of 9 thymoma patients without clinically significant pemphigus had intercellular epithelial antibodies, suggesting that parathymic pemphigus may be caused by autoantibody production related to thymoma (26). In the present case, total thymectomy relieved the cutaneous lesions and reduced the serum anti-Dsg 1 antibody index value, a recently developed diagnostic test specific for PF. These facts revealed a direct connection between the thymoma and PF in our patient.

Patients who have a thymic tumor without parathymic syndromes usually undergo thymic resection. Two case reports in Japan described patients who developed pemphigus long after thymectomy (15, 16). Takeuchi et al (16) reported pemphigus

Table 2. Reported Cases of Thymoma with Pemphigus in Japan Since 1988

Age	Gender	Pemphigus	Preceding manifestation	Preceding interval (yr)	MG	Immuno-suppression	Thymectomy/Influence on pemphigus	Reference
39	M	V	S		(–)	(–)	(–)	(13)
40	F	E	S		(+)	(–)	(+)/I	(14)
43	F	V	T	20	(–)	(–)	(–)	(15)
46	F	E	T	8	(–)	(+)	(+)	(16)
55	F	V	S		(–)	(–)	(+)/A	(17)
56	M	V	S		(+)	(+)	(+)/A	(18)
63	F	V	P	8	(–)	(+)	(+)/I	(19)
66	F	V	NA		NA	NA	NA	(20)
70	F	F	S		(+)	(–)	(+)/NA	(21)
73	F	E	S		(–)	(–)	(+)/NC	(22)
75	F	F	S (?)		(–)	(–)	(+)/I	The Present Case

S: simultaneously, T: thymoma, MG: myasthenia gravis, P: pemphigus, V: pemphigus vulgaris, E: pemphigus erythematosus, F: pemphigus foliaceus, (–): not operated, (+): operated, NA: not available, I: improved, NC: no change, A: aggravated.

which manifested 8 years after thymectomy for MG, leading them to conclude that thymectomy can alter autoimmune regulation and induce pemphigus.

Treatment of pemphigus includes systemic glucocorticoids, cyclosporin, azathioprine, cyclophosphamide, gold, and plasmapheresis (27). These immunosuppressive therapies are indispensable, especially for PV, which, unlike PF, can be life-threatening. In the present case, glucocorticoids were only used topically and failed to relieve the PF. Younus and Ahmed claimed that immunosuppressive treatment for pemphigus in patients with non-thymic malignancies preceded by pemphigus may have caused the neoplasms by altering immunity to tumor cells, but they did not assess in detail the 5 thymic neoplasm cases preceded by pemphigus (12). Among the recent reports in Japan, pemphigus preceded the neoplasm in only one case. Sasaki et al reported a case in which the thymoma was detected 8 years after the onset of the pemphigus (19). The patient had been treated with prednisolone and sodium aurothiomalate for at least 7 years, suggesting that immunosuppression may have been a predisposing factor in inducing the thymoma.

Thymectomy for thymoma-related pemphigus has been controversial, and the clinical outcome of the patients reported in Japan has varied. Thymectomy was performed in 7 of the most recent 9 cases in Japan in which thymoma existed at the time pemphigus was diagnosed. Surgery was not performed in 2 cases because the patients died due to the sequelae of pemphigus immediately after the diagnosis was made. Improvement in cutaneous lesions after thymectomy was seen in 3 of the cases but not in the remaining 4; 2 of these 4 the pemphigus was exacerbated. One case was controlled by increasing the prednisolone dosage during the postoperative exacerbation (17), but the other patient died soon after thymectomy because of exacerbation of the pemphigus and opportunistic infection (18). In the present case, improvement of the pemphigus was confirmed on the basis of the cutaneous manifestations as well as the sepecific serological marker, anti-Dsg 1 antibody. This is the first case report confirming the serological influence of thymectomy on thymoma-related pemphigus by utilizing this recently established marker. Thymectomy can be a reasonable treatment for pemphigus-accompanied thymoma even though the pemphigus may become aggravated after the resection, because thymic carcinoma cannot be ruled out preoperatively (28). Exacerbation of the clinical course and increases in anti-acetyl choline receptor antibody titer after thymectomy are known to occur more frequently in MG patients with thymoma than in those without thymoma (29). Thymectomy, however, is usually performed in thymoma-related MG patients after appropriate control of MG by intensified immunosuppressive therapy (29). We recommend that thymectomy for pemphigus associated with thymoma be considered on an individual basis while informing patients of the possible outcome of both the thymoma and pemphigus. Further investigation involving more patients is necessary to elucidate the efficacy of thymic resection and the appropriate perioperative management of patients with pemphigus and thymoma.

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