The incidence of internal malignancies in autoimmune bullous diseases

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Autoimmune bullous diseases are classified into pemphigus and pemphigoid. Pemphigus is designated as incurable disease by the Ministry of Health, Labor and Welfare, and it is said that pemphigus is difficult to care and can be fatal. The clinical course of bullous pemphigoid (BP) is better than that of pemphigus. However, as to the incidence of internal malignancies, it is well known that there is a significant difference between the two diseases. As the incidence of internal malignancies is high in BP, it is described in textbooks that patients with BP should be followed by a detailed screening for internal malignancies.

We investigated the incidence of internal malignancies in 204 Japanese patients with autoimmune bullous disease who visited Tokai University Hospital in Kanagawa, Japan. We found that the incidence of internal malignancies was 11.2% in patients with pemphigus and 10.4% in patients with BP. Among pemphigus variants, the incidence was as high as 20% for pemphigus erythematosus. No relationship was found between malignancies and the severity of the autoimmune bullous diseases.

Therefore it is clinically important to carry out a detailed screening for internal malignancies in patients with pemphigus as well as in patients with BP.

Key words: autoimmune bullous diseases, internal malignancy, pemphigus, bullous pemphigoid, BP

INTRODUCTION

Autoimmune bullous diseases are rare. In recent years, however, their increase has been a concern. Clinically, they are classified roughly into pemphigus and pemphigoid. Pemphigus is designated as incurable disease by the Ministry of Health, Labor and Welfare, and is said to be difficult to care and fatal. Its diagnosis, treatment and other aspects were studied [1]. Recent progress in molecular biology and immunological techniques encourages that the classification of autoimmune bullous diseases be subdivided.

The clinical course of bullous pemphigoid (BP) is better than that of pemphigus [2]. However, as to the incidence of internal malignancies, it is well known that there is a significant difference between the two diseases. Because the incidence of internal malignancies is high in BP [3-4], textbooks describe that patients with BP should be followed by a detailed screening for internal malignancies. Through clinical consultations with pemphigus patients, we noticed that the incidence of internal malignancies might be not so low in those patients. Actually, an epidemiological investigation was presented at a group conference of the Ministry of Health, Labor and Welfare of Japan, reporting that the incidence of internal malignancies was 5.0% in pemphigus and 5.8% in BP [3]. The incidence of internal malignancies in BP was higher than in pemphigus.

To assess the association of malignancies with autoimmune bullous diseases, we conducted a retrospective study in patients with the disease who visited our hospital and determined the incidence of malignancies.

SUBJECTS AND METHODS

1. Subjects

We reviewed medical records for all patients with autoimmune bullous diseases who visited Department of Dermatology, Tokai University Hospital (Kanagawa, Japan) between February 1975 and January 2006. The autoimmune bullous diseases we studied included pemphigus vulgaris, pemphigus vegetans, pemphigus foliaceus, pemphigus erythematosus, paraneoplastic pemphigus (PNP) and BP.

Table 1 shows demographic characteristics of the patients. Medical records were available for 204 patients with autoimmune bullous diseases. The patients con-

Table 1 Demographic characteristics of the study patients.

	Number of patients	Age in years** (range)
Pemphigus*	89	57.2±17.9 (16-87)
Male	52	55.5±15.8
Female	37	59.6±18.8
Bullous pemphigoid	115	76.2±10.7 (40-93)
Male	53	75.1±11.1
Female	62	77.1±10.4

* Types of pemphigus were pemphigus vulgaris (50), pemphigus vegetans (1), pemphigus foliaceus (27) pemphigus erythematosus (10) and paraneoplastic pemphigus (1).

** First visit age. Data are expressed as means ± standard deviation.

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sisted of 89 with pemphigus (50 cases with pemphigus vulgaris, 1 case with pemphigus vegetans, 27 cases with pemphigus foliaceus, 10 cases with pemphigus erythematosus, 1 case with PNP) and 115 with BP. Two patients were complicated with pemphigus foliaceus and BP.

The analysis included internal malignancies found either during the course or before the diagnosis of autoimmune bullous disease.

2. Methods

The incidence of internal malignancies was calculated and analyzed by age groups and types of autoimmune bullous disease. For the analysis by age groups, we identified the age of detection of internal malignancy for patients with internal malignancies and the age of first visit to our hospital for the treatment of the autoimmune bullous disease for patients without malignancies. The incidence for the patients with pemphigus or BP was compared with that for the general Japanese population, which was estimated based on the outpatient visit rate in 2002 [5] and the national population by age groups in 2004 [6] reported in *Annual Statistical Report of National Health Conditions 2005*. We also studied types of concurrent internal malignancies and a relationship between malignancies and the severity of the autoimmune bullous diseases. The severity was assessed according to the criteria for assessing the severity of pemphigus established by the Ministry of Health and Welfare [7].

RESULTS

1. Incidence of internal malignancies

The incidence of malignancies for BP patients has been reported to be higher than that for the general population [8]. We studied in details the association of internal malignancies with BP. Table 2 lists all the patients with BP with malignancies. Of the 115 patients, 12 (10.4%) had malignancies.

Since the incidence of internal malignancies was high not only for the patients with BP but also for the patients with pemphigus, we studied in details the association of internal malignancies with pemphigus in the same manner as that for BP. Table 3 lists all the patients with pemphigus with malignancies. Ten (11.2%) of the 89 patients had malignancies.

2. Age of first visit

Figure 1 illustrates the incidence of internal malignancies by age groups in the patients with pemphigus, the patients with BP, and the general population as a control. Under 50 years of age, the incidence was 6.5% for the patients with pemphigus and 33.3% for the patients with BP. Between the ages of 50 and 59 years, the incidence was 7.1% for the patients with pemphigus and 0% for the patients with BP. Between the ages of 60 and 69 years, the incidence was 15.8% for the patients with pemphigus and 11.8% for the patients with BP. Over 70 years of age, it was 16.0% for the patients with pemphigus and 10.2% for the patients with BP.

3. Gender

In BP, the incidence of malignancies was higher for men than for women, with no statistically significant difference (15.1% [8/53] vs. 6.5% [4/62]). The age of first visit was 77.7 ± 6.9 years for all BP patients with malignancies, 80.8 ± 5.8 years for men, and 71.5 ± 4.1 years for women. In pemphigus, the incidence of malignancies by sex was 15.4% (8/52) for men and 5.4% (2/37) for women, with no statistically significant difference. The age of first visit was 64.2 ± 13.4 years for all pemphigus patients with malignancies, 66.9 ± 13.3 years for men, and 53.5 ± 9.2 years for women.

4. Severity

The severity was assessed according to the criteria for assessing the severity of pemphigus established by the Ministry of Health and Welfare [7].

Figure 2 compares the severity of BP between

Table 2 Bullous pemphigoid patients with internal malignancies.

Case	Year of Onset of Bullous Pemphigoid	Sex*	First Visit Age	Severity of Bullous Pemphigoid†	Type of Malignancy	Age of Malignancy Detection	Other Skin Disorder
1	1986	Female	71	Unknown	Bladder cancer	Unknown	
2	1993	Male	90	Mild	Gastric cancer	91	
3	1995	Female	71	Moderate	Gastric cancer	71	
4	1997	Male	82	Moderate	Prostate cancer	81	Pemphigus foliaceus
5	1998	Female	67	Mild	Left renal pelvic cancer	69	
6	1999	Male	75	Unknown	Laryngeal cancer	75	
7	1999	Male	76	Mild	Gastric cancer	74	
8	2001	Male	87	Unknown	Colorectal cancer	Unknown	
9	2002	Female	77	Mild	Breast cancer	64	
10	2002	Male	84	Unknown	Lung cancer	72	
11	2004	Male	76	Mild	Gastric cancer	76	
12	2004	Male	76	Moderate	Rectal cancer	49	

*Incidence of internal malignancies by sex is 15.1% (8/53) for male and 6.5% (4/62) for female.

† Severity of bullous pemphigoid was assessed according to the First and Second National Surveys on Pemphigus Severity Assessment Criteria (Draft Revision) Annual Report From Intractable Skin Disease Studygroup, Ministry of Health and Welfare Designated Skin/Connective Tissue Disease Research Group, 1997. S. Ikeda, *et al.* [7].

Table 3 Pemphigus patients with internal malignancies.

Case No.	Year of Onset of Pemphigus	Type of Pemphigus*	Sex†	First Visit Age	Diagnostic Method for Pemphigus‡	Severity of Pemphigus§	Type of Malignancy	Age of Malignancy Detection	Other Skin Disorder
1	1977	PE	Male	53	DIF	Mild	Lung cancer	65	
2	1985	PV	Male	59	ELISA	Mild	Hepatocellular carcinoma and Esophageal cancer	66/69	
3	1988	PE	Male	72	DIF	Unknown	Pancreatic cancer	72	
4	1993	PF	Male	69	IIF	Mild	Esophageal cancer	69	
5	1998	PF	Male	82	Immunoblot	Moderate	Prostate cancer	81	Bullous pemphigoid
6	1999	PNP	Male	45	Immunoblot	Unknown	Malignant lymphoma	41	
7	1999	PV	Male	81	DIF	Mild	Bladder cancer	81	
8	1999	PF	Male	74	Immunoblot	Moderate	Bladder cancer	75	
9	2000	PF	Female	47	ELISA	Unknown	Gastric cancer	48	
10	2005	PV	Female	60	ELISA	Moderate	Breast cancer	59	

* Abbreviations are: PE, pemphigus erythematosus; PV, pemphigus vulgaris; PF, pemphigus foliaceus; PNP, paraneoplastic pemphigus.

† Incidence of internal malignancies by sex was 15.4% (8/52) for male and 5.4% (2/37) for female.

‡ Abbreviations are: DIF, direct immunofluorescence; IIF, indirect immunofluorescence; ELISA, enzyme-linked immunosorbent assay.

§ Severity of Pemphigus was assessed according to the First and Second National Surveys on Pemphigus Severity Assessment Criteria (Draft Revision) Annual Report From Intractable Skin Disease Studygroup, Ministry of Health and Welfare Designated Skin/Connective Tissue Disease Research Group, 1997. S. Ikeda, *et al.* [7].

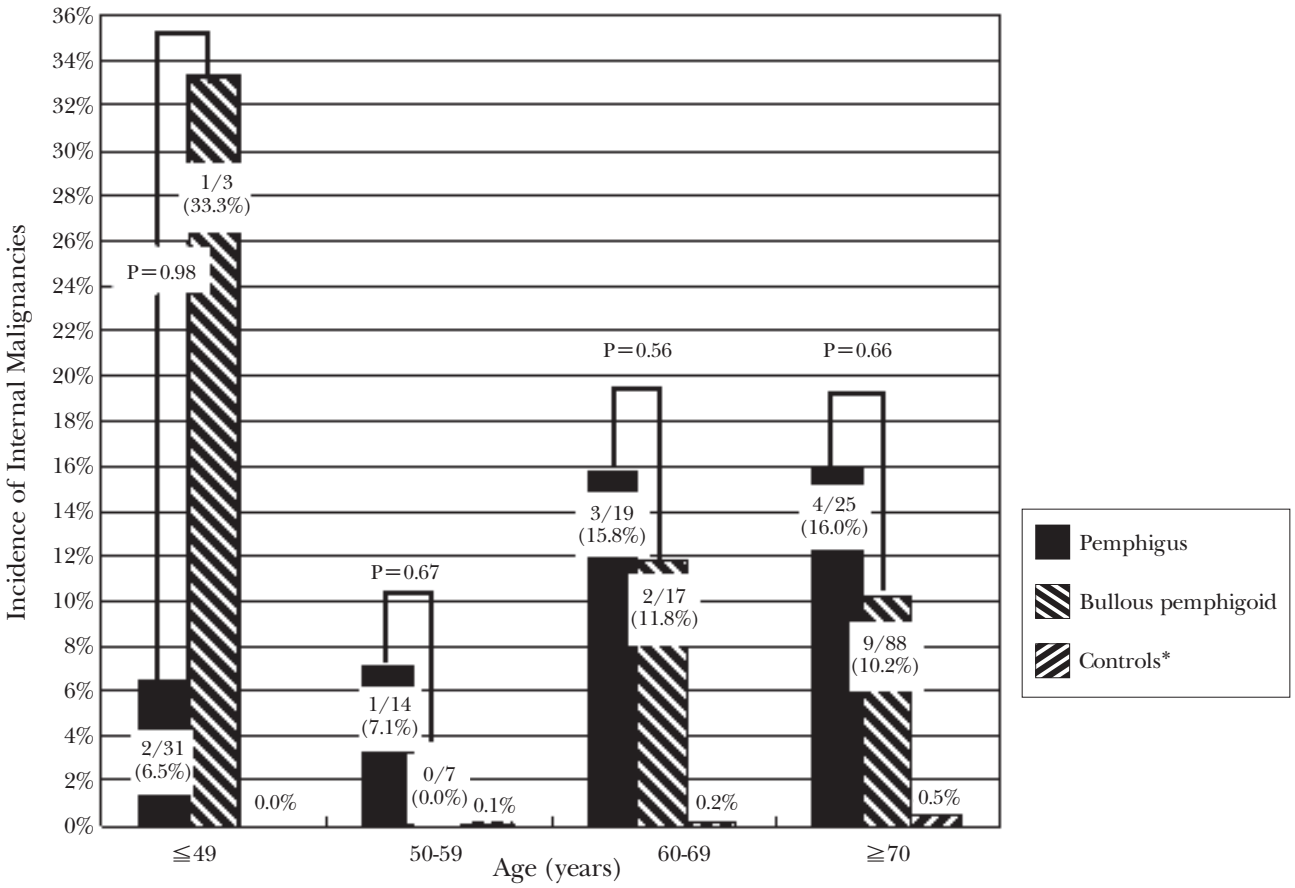

Fig. 1 Incidence of internal malignancies by age groups.
Patients with pemphigus or pemphigoid were groups according to the first visit age.
*Data for controls are estimates based on the outpatient visit rate in 2002 [5] and the Japanese population in 2004 [6] reported in *Annual Statistical Report of National Health Conditions*.

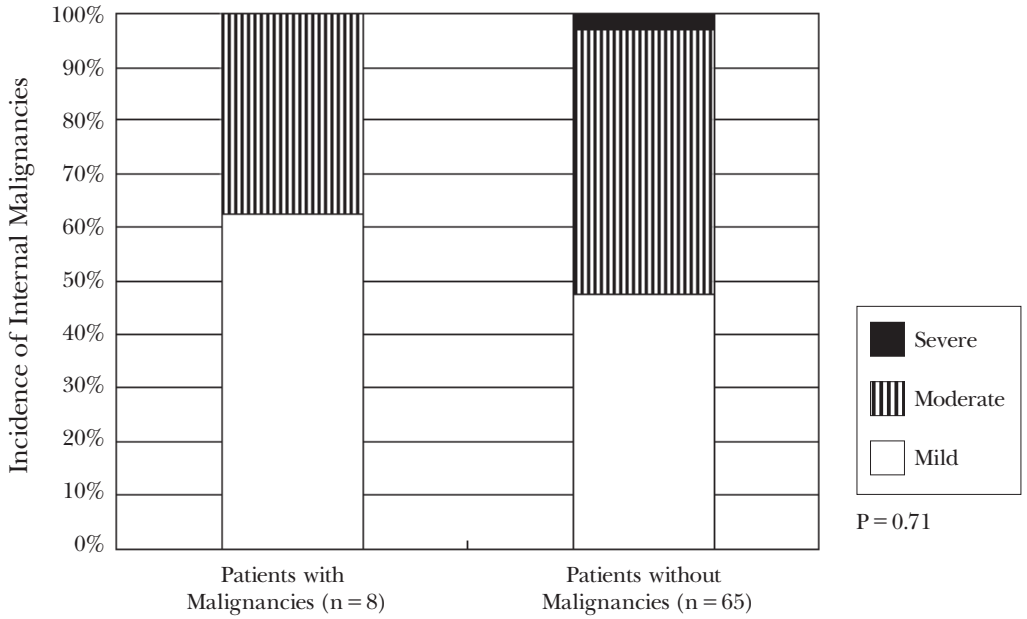

Fig. 2 Relationship between internal malignancies and severity of bullous pemphigoid.
Severity was assessed according to the First and Second National Surveys on Pemphigus Severity Assessment Criteria (draft revision) [7].

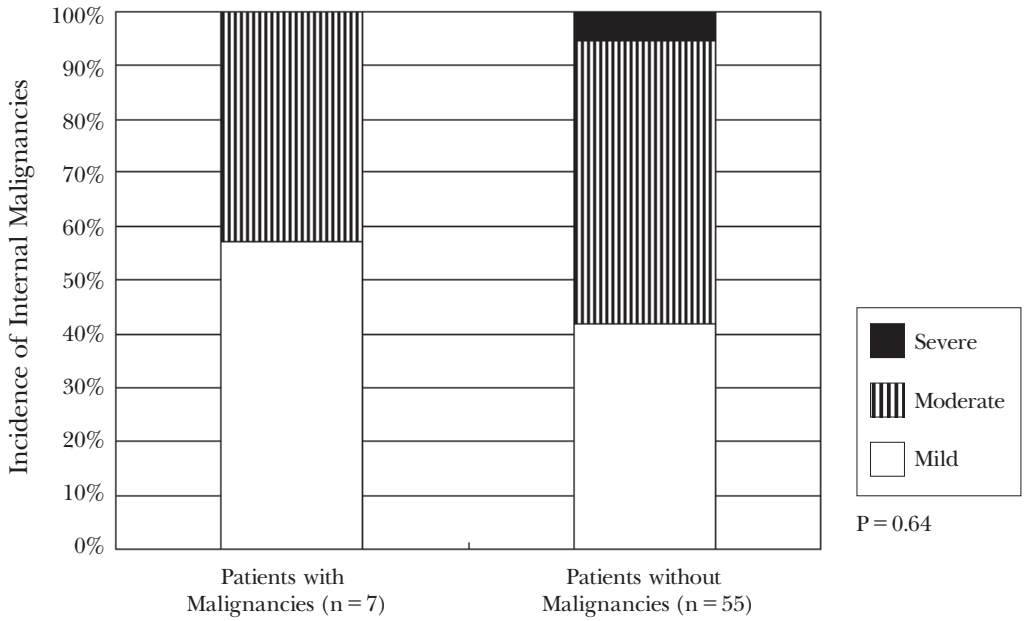

Fig. 3 Relationship between internal malignancies and severity of pemphigus.
Severity was assessed according to the First and Second National Surveys on Pemphigus Severity Assessment Criteria (draft revision) [7].

patients with or without internal malignancies. The comparison showed no apparent relationship between the severity and malignancies.

Figure 3 illustrates a comparison of the severity of pemphigus between patients with or without internal malignancies. The comparison showed no apparent relationship between the severity and malignancies.

After the treatment of internal malignancies, the skin symptom showed no improvement.

5. Type of pemphigus

Figure 4 shows the incidence of internal malignancies by types of pemphigus in 89 patients whose disease types were documented. Understandable for the definition of the disease, the incidence was the highest for PNP. The incidence was the second highest for pemphigus erythematosus (20%).

6. Type of internal malignancies

The most common internal malignancy in BP was

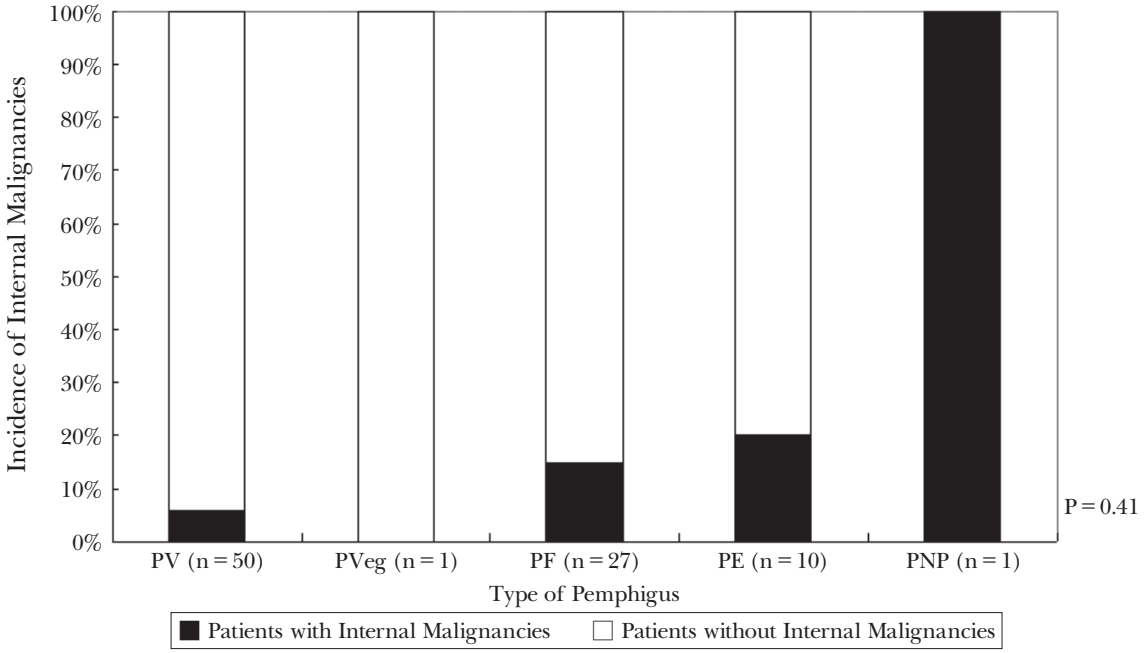

Fig. 4 Relationship between internal malignancies and types of pemphigus.
Abbreviations are: PV, pemphigus vulgaris; PVeg, pemphigus vegetans; PF, pemphigus foliaceus; PE, pemphigus erythematosus; PNP, paraneoplastic pemphigus.

gastric cancer (four patients). In pemphigus, esophageal and bladder cancers developed in two patients each, and the most frequently affected organ system was the gastrointestinal system (four patients).

7. Relationship between the onset of bullous disease and internal malignancies

Internal malignancies developed after the onset of BP in two patients (16.7%), coincidentally with the disease in five (41.7%), and before the onset of the disease in five (41.7%).

Internal malignancies developed after the onset of pemphigus in six patients (54.5%), coincidentally with the disease in three (27.3%), and before the onset of the disease in two (18.2%).

8. Titers of autoantibodies

There was no statistically significant difference between the patients with or without internal malignancies.

In PNP patient, there was no positive immunofluorescence reaction and no antibody for desmoglein 1 and desmoglein 3 in enzyme-linked immunosorbent assay, but there were antibodies for proteins of about 180 kDa, 190 kDa and 210 kDa [9].

DISCUSSION

We determined the incidence of internal malignancies in 89 patients with pemphigus and 115 patients with BP. The incidence was 11.2% for the patients with pemphigus and 10.4% for the patients with BP. Our study found significantly higher incidence than the report of Ogawa *et al.* in 1993 [3] (5.0% in pemphigus and 5.8% in BP). Possible reasons for the observed difference include, among others, the improvement of the accuracy of the diagnostic imaging and tumor markers and the regional differences in the incidence of internal malignancies.

For pemphigus, the incidence was 6.5% for the patients under 50 years of age, 7.1% for those aged 50 to 59 years, 15.8% for those aged 60 to 69 years, and 16.0% for those aged 70 years or older. For BP, the incidence was 33.3% for the patients under 50 years of age, 0% for those aged 50 to 59 years, 11.8% for those aged 60 to 69 years, and 10.2% for those aged 70 years or older. These results indicate that the incidence for BP was lower than that for pemphigus in patients aged 50 years or older. It is noteworthy that internal malignancies were found in approximately 15% of patients with pemphigus aged 60 years or older and in 6.5% of the patients under 60 years of age. Patients with pemphigus should thus be screened thoroughly to detect potential internal malignancies regardless of age. Analysis of the incidence of internal malignancies by types of pemphigus showed that the incidence was as high as 20% for pemphigus erythematosus. No relationship was noted between malignancies and the severity of the autoimmune bullous diseases.

In conclusion, the diagnosis of pemphigus, particularly pemphigus erythematosus, should be followed by a detailed screening for internal malignancies regardless of age and severity of pemphigus.

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