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Malignancies in Pemphigus and Pemphigoid Diseases

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TO THE EDITOR

Pemphigus and pemphigoid diseases comprise a heterogeneous group of diseases that are immunopathologically characterized by autoantibodies against structural proteins of the desmosome and dermo–epidermal junction, respectively. The clinical picture typically shows blisters and erosions on the skin and/or surface-close mucous membranes (Stanley and Amagai, 2006; Schmidt and Zillikens, 2013). Bullous pemphigoid (BP) is the most frequent of these diseases with a disease onset in the late seventies and an incidence of 150–300/millions/year in the population of 80 years and older (Langan *et al.*, 2008). Its incidence has at least doubled in the last decade and the 1-year mortality ranges from 20 to 40%, which is about two to three times higher compared with age- and sex-matched controls (Langan *et al.*, 2008; Joly *et al.*, 2012; Schmidt and Zillikens, 2013). Various case–control studies revealed conflicting data about the association of BP with malignancies. Two case–control studies >1,700 BP patients from Sweden and Japan only revealed a low association with gastric cancer in the Japanese patients (Lindelöf *et al.*, 1990; Ogawa *et al.*, 1995). In contrast, numerous case reports describe BP patients with various associated malignancies, and recently Ong *et al.* reported an increased risk of BP in patients with kidney cancer, laryngeal cancer, and leukemia (Ong *et al.*, 2014). Although no data about malignancies are available for pemphigus vulgaris and pemphigus foliaceus, the association with malignancies is undisputed in two rare autoimmune blistering diseases, paraneoplastic pemphigus, and anti-laminin 332 pemphigoid (Anhalt *et al.*, 1990; Egan *et al.*, 2001; Bernard *et al.*, 2013). The aim of the present study was to investigate the association between autoimmune bullous diseases and cancer in a large German cohort.

Data were extracted from the database of a major health insurance company in Germany, the Techniker Krankenkasse. All 8.3 million health-insured subjects from 2008 to 2011 were analyzed on the basis of the ICD-10-GM 2011 classification. Autoimmune bullous disease patients' data were compared with an at least 5-fold higher number of age- and sex-matched controls randomly selected from the database.

Initially, associations between each disease and the 13 groups of malignancies mentioned in chapter 3 of ICD-10 (C00-14, C15-26, C30-39, C40-41, C43-44, C45-49, C50, C51-58, C60-63, C64-68, C69-70, C73-75, and C81-96) were analyzed. In case of significance, a fine analysis was performed. *P*-values were calculated by Fisher's exact test and confidence intervals according to Wilson's procedure.

An association of BP, pemphigus vulgaris, and epidermolysis bullosa acquisita with hematological malignancies was observed (Table 1). Fine analyses revealed Hodgkin disease (C81; OR 4.2 (1.90–8.9); $P<0.01$), non-follicular lymphoma (C83; OR 3.80 (1.90–7.5); $P<0.01$), mature T/NK-cell lymphomas (C84; OR 6.90 (3.1–16.0); $P<0.001$), unspecified types of non-Hodgkin

Table 1. Association of pemphigus and pemphigoid diseases with hematological malignancies

	Patient characteristics				Controls		OR (95% CI)	*P*-value	%[1]
	Number	Age (years) Median	Sex ratio (f: m)	Events	Number	Events			
Bullous pemphigoid	1,743	71	1:1.17	117	10,141	275	2.55 (2.07–3.13)	< 0.001	49
Pemphigus vulgaris	860	54	1.11:1	34	5,142	115	2.10 (1.40–3.03)	0.003	71
Pemphigus foliaceus	103	57	0.84:1	4	588	23	1.68 (0.48–4.78)	0.64	NA
Pemphigoid gestationis	126	33	n. a.	1	933	8	0.92 (0.06–4.63)	1	NA
Mucous membrane pemphigoid	251	63	1.9:1	3	1,386	40	0.50 (0.14–1.25)	0.25	NA
Epidermolysis bullosa acquisita	106	59	1.12:1	9	606	14	3.46 (1.48–7.66)	0.005	NA
Lichen sclerosus et atrophicans	27,021	55	4.5:1	504	158,329	2,812	1.05 (0.95–1.15)	0.33	45

Abbreviations: CI, confidence interval; f, female; m, male; NA, not applicable; OR, odds ratio.
[1]Percentage of patients, in whom the malignancy preceded the diagnosis of the autoimmune bullous disease.

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Table 2. Association of pemphigus and pemphigoid diseases with non-hematological malignancies

Non-hematological malignancies (ICD-10)	Events (patients)	Events (controls)	OR (95% CI)	*P*-value	%[1]
Pemphigus vulgaris					
Oropharyngeal cancer (C10)	8	7	7.21 (2.68–19.9)	<0.001	20
Gastrointestinal cancer (C15-C26)	53	143	2.56 (1.85–3.46)	<0.001	NA
Colon cancer (C18)	32	78	2.44 (1.61–3.62)	<0.001	21
Pemphigus foliaceus					
Non-melanoma skin cancer (C44)	17	40	2.45 (1.43–4.04)	0.002	67
Mucous membrane pemphigoid					
Non-melanoma skin cancer (C44)	37	113	1.80 (1.25–2.5)	0.001	69
Eye and adnexa cancer (C69)	7	0	11.47 (3.32–48.11)	<0.001	NA
Lichen sclerosus et atrophicans					
Cancer of female genital organs (C51–C58)	733	2,049	2.1 (1.93–2.28)	<0.001	43
Cancer of male genital organs (C60–C63)	70	150	2.73 (2.04–3.61)	< 0.001	63

Abbreviations: CI, confidence interval; NA, not applicable; OR, odds ratio.
[1]Percentage of patients, in whom the malignancy preceded the diagnosis of the autoimmune bullous disease.

lymphoma (C85; OR 2.60 (1.60–3.9); $P<0.001$), myeloid leukemia (C92; OR 5.70 (1.90–17.0); $P=0.01$), and leukemia of unspecified cell type (C95; OR 2.70 (1.40–5.1); $P=0.03$) to be associated with BP. Epidermolysis bullosa acquisita was associated with mature T/NK-cell lymphoma (C84; OR 72.42 (4.48–43,553.96); $P=0.03$). Associations with non-hematological malignancies are also shown in Table 2.

Lichen sclerosus, an inflammatory dermatosis not mediated by autoantibodies, served as control. While no associations with hematological malignancies are known for this disease, cancer of genital organs and of the skin frequently arises in lichen sclerosus (Table 2).

Here we provide evidence for increased frequencies of malignancies in several autoimmune bullous diseases. The percentages of patients with hematological malignancies were 8.4% among epidermolysis bullosa acquisita, 6.7% among BP, and 3.9% among pemphigus vulgaris patients.

Latter association was previously shown with paraneoplastic pemphigus (Anhalt *et al.*, 1990). However, pemphigus vulgaris and paraneoplastic pemphigus diseases are clearly differentiated by ICD-10 codes (L10.0 and L10.8).

As in about half of the BP patients, the hematological malignancy preceded the diagnosis of BP, it appears unlikely that the autoimmune disease had triggered the malignancy. Interestingly, no association with non-hematological malignancies was seen in BP. These data support the results of two large case–control studies (Lindelöf *et al.*, 1990; Ogawa *et al.*, 1995) and indicate that the assumption by numerous case reports that reported such an association and our impression as treating physicians may rather result from the high rate of malignancies in this elderly patient population.

Furthermore, oropharyngeal and colon carcinomas were present in 0.9% and 3.7% of pemphigus vulgaris patients, respectively. Of note, the two carcinomas preceded the diagnosis of pemphigus vulgaris in only 20% of patients, indicating that the autoimmune disease may have triggered the malignancy (Table 2). This notion is somehow corroborated by the observation that pemphigus foliaceus (in which mucous membrane are not involved) was not associated with oropharyngeal and gastrointestinal malignancies. As pemphigus foliaceus and vulgaris usually receive the same immunosuppressive therapy, it appears unlikely that the carcinomas in pemphigus vulgaris were triggered by the immunosuppressive medication. However, in all other autoimmune bullous diseases, no clear temporal relationship with the malignancies was observed favoring the idea of a so far unknown immunological or genetic third factor that triggers both the malignancy and the autoimmune disease.

Accordingly, an association with malignancies of the eye and its adnexa was only found in the single autoimmune bullous disease with potential eye involvement—mucous membrane pemphigoid (Table 2). In fact, we and others have previously described the occurrence of malignant tumors of the eye with an ocular involvement in these patients (Robinson *et al.*, 2006; Riederle *et al.*, 2009).

Non-melanoma skin cancer was linked with pemphigus foliaceus and mucous membrane pemphigoid in 16.5% and 14.7% of patients, respectively (Table 2). Interestingly, in most patients, the skin cancer was diagnosed before the autoimmune disease speaking against the hypothesis that the erosions, blisters, and the subsequent regeneration process may have triggered the skin cancer.

The validity of the ICD-10-derived diagnoses was probed by data from patients with pemphigoid gestationis and lichen sclerosus. As expected, in pemphigoid gestationis, a pemphigoid disorder occurring during pregnancies or the postpartum period (Schmidt and

Zillikens, 2013), no associated malignancy was observed. In contrast, in lichen sclerosus, carcinomas of the genitalia and the skin were revealed (Powell and Wojnarowska, 1999). A possible drawback of this study is its reliance on the ICD-10 coding of doctors from different specialities. Although the large majority of autoimmune bullous diseases are diagnosed by dermatologists, coding of these disorders by non-dermatologists might have led to mistakes. On the basis of the coding of pemphigoid gestationis in one man and four female patients older than 50 years, the false-coding rate was estimated to be 4%.

The present findings will be relevant for the future care of patients with autoimmune bullous disorders. Regardless of the reason for the higher incidence of cancer in some of these diseases, an increased awareness in combination with regular differential blood counts and inspection of the entire skin, as well as routinely performed gastro- and coloscopy in patients with pemphigus vulgaris might be helpful to detect the associated malignancies as early as possible in the majority of patients.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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The Kindler Syndrome: A Spectrum of *FERMT1* Mutations in Iranian Families

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TO THE EDITOR

The Kindler syndrome (KS; OMIM173650) is a rare autosomal recessive disorder characterized by trauma-induced blistering, cutaneous atrophy, and progressive poikiloderma, in association with mucosal inflammation (Kindler, 1954; Lai-Cheong and McGrath, 2010; Has *et al.*, 2011). Some individuals also suffer from photosensitivity, which tends to lessen with advancing age. Marked skin atrophy, the hallmark of the disease, develops early in life particularly on the dorsal aspects of the hands and feet and becomes generalized in most cases by adolescence. Other clinical features include mucosal stenosis, gastrointestinal symptoms, and increased risk for non-melanoma skin cancer, with development of squamous cell carcinomas in acral skin and the mouth with considerable phenotypic variability (Cardin-Langlois *et al.*, 2010; Has *et al.*, 2010; Lai-Cheong and McGrath, 2010; Has *et al.*, 2011). Histopathology of the skin shows hyperkeratosis, epidermal atrophy, loss of rete ridges, and focal vacuolization of the basal layer of the epidermis, consistent with poikiloderma. Transmission electron microscopy of the non-blistered skin demonstrates reduplication of the basal lamina with focal interruptions of the lamina densa, a diagnostic feature that can be demonstrated by immunofluorescence staining of the skin with an anti-type IV or type VII collagen antibody or by transmission electron microscopy.

Abbreviations: EB, epidermolysis bullosa; KS, the Kindler syndrome

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