Our Dermatology Online

Original Article

Pemphigus and cancer: A single-center experience over 30 years in Morocco

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ABSTRACT

Background: The aim of this study was to investigate the association between pemphigus and cancer and to analyze the characteristics of pemphigus in which a neoplasm occurs. **Materials and Methods:** This was a retrospective, descriptive study conducted at the Dermatology Department of Ibn Sina Hospital in Rabat from January 1993 to December 2022, including all pemphigus cases in which cancer was diagnosed before, during, or after the onset of pemphigus. **Results:** Among 302 pemphigus cases, 13 patients presented an associated cancer (4,3%). Only one patient had a paraneoplastic pemphigus. There was an increased incidence of various solid cancers (11/13) in deep pemphigus types yet without temporal relationship. When hematological malignancy occurred (3/13), it was mainly non-lymphoproliferative and preceded deep pemphigus types with good prognosis. Patient comorbidities and immunosuppressive treatments did not influence the onset of cancer. **Conclusion:** Our manuscript suggests an increased incidence of solid cancers in deep pemphigus subtypes, independently of the timeline of the latter onset. These pemphigus cases carry a good prognosis.

Key words: Pemphigus, Cancer, Paraneoplastic pemphigus, Paraneoplastic autoimmune multiorgan syndrome

INTRODUCTION

Paraneoplastic pemphigus (PNP) was first described in 1990 by Anhalt et al. as the co-existence of a neoplasm and polymorphic mucocutaneous clinical manifestations and the histopathological aspect of pemphigus, bullous pemphigoid, and erythema multiform. It was initially considered a unique autoimmune blistering disease secondary to autoantibodies directed against desmoplakin I and bullous pemphigoid major antigen (BP230) in immunology, in addition to IgG and C3 deposits along the dermo-epidermal junction and between keratinocytes [1].

However, since the initial publication, numerous atypical cases have been reported that do not meet the proper criteria of PNP [2]. This concept has, therefore, evolved into paraneoplastic autoimmune multi-organ syndrome (PAMS) [3,4], which is still distinct from traditional pemphigus associated with cancers.

Herein, we report a case series of pemphigus with underlying neoplasms at the Dermatology Department of Ibn Sina Hospital in Rabat during the last 30 years. The aim of the study was to investigate the association between pemphigus and cancer and to analyze the characteristics of pemphigus in which a neoplasm occurs.

MATERIALS AND METHODS

We performed a retrospective, descriptive study including all pemphigus cases associated with a neoplasm at the Dermatology Department of Ibn Sina Hospital in Rabat over 30 years (between January 1993 and December 2022). We included all pemphigus cases in which cancer was diagnosed before, during, or after the onset of pemphigus.

How to cite this article: Karrakchou B, Fliti A, Meziane M, Ismaili N, Hamada S, Benzekri L, Senouci K. Pemphigus and cancer: A single-center experience over 30 years in Morocco. Our Dermatol Online. 2023;14(4):361-366.

Submission: 19.01.2023; **Acceptance:** 02.07.2023

DOI: 10.7241/ourd.20234.4

RESULTS

Epidemiologic Findings

We collected thirteen cases of pemphigus associated with cancer among 302 pemphigus cases hospitalized during the last 30 years [5], which corresponded to 4.3% (Table 1).

There were six males and seven females, yielding a sex ratio of 0.9. The mean age on diagnosis was 61.7 years (with extremes ranging from 45 to 81 years).

Regarding cardiovascular comorbidities, 3/13 cases presented hypertension, 5/13 were diabetic, 2/13 were overweight, 1/13 was moderately obese, and 1/13 was a chronic smoker.

Auto-immunity was associated in 1/13 patient (Hashimoto thyroiditis), and 1/13 patient suffered from chronic urticaria.

Concerning infectious diseases, 1/13 presented COVID-19, 1/13 suffered from acute viral pericarditis, 1/13 developed angiocholitis, and 1/13 had been cured of a pulmonary hydatid cyst.

Neurological comorbidities were present in 2/13 patients (epilepsy and mental retardation).

Clinical Findings

The predominant clinical form was deep pemphigus, present in 6 patients, mainly represented by pemphigus vulgaris (4/13). There was only 1/13 case of paraneoplastic pemphigus.

The PDAI was mainly moderate (10/13), with extremes ranging from 14 to 188. The highest PDAI was noticed in paraneoplastic pemphigus.

Pruritus was present in six cases.

Among the thirteen patients, five patients did not have mucosal involvement. When the mucosa was affected, it was mainly the buccal mucosa (6/8).

Regarding additional neoplasms, either solid cancers or hematological ones, there was a predominance of non-hematological cancers in 10/13 patients. Indeed, 2/13 had papillary thyroid carcinoma, 2/13 suffered from colon adenocarcinoma, 2/13 were cured of squamous cell carcinoma (skin, nail, and palatin), 1/13 was treated for dermatofibrosarcoma protuberans, 1/13 had papillary cystadenocarcinoma of the ovary, 1/13 suffered from breast adenocarcinoma, 1/13 had prostate carcinoma, and 1/13 was treated for neuroendocrine small bowel tumor.

Among hematological ones, the only lymphoproliferative disease of the series was associated with paraneoplastic pemphigus (B-cell chronic lymphocytic leukemia).

Pemphigus lesions appeared before the onset of cancer in 4 patients (patients 2, 7, 8, and 12) after a mean time of 6 years (1 to 10 years). All were under oral corticosteroids (2 mg/kg/day), and patient 8 was under additional azathioprine (2 mg/kg/day). Nine patients developed cancer before the diagnosis of pemphigus, including the case with paraneoplastic pemphigus (patients 1, 3, 4, 5, 6, 9, 10, 11, and 13), with a mean time of 2.4 years. One patient (patient 4) had four concomitant neoplasms (three squamous cell carcinomas of the skin and nails and one myelodysplasia).

Histopathologic and Immunologic Findings

In 11 cases out of the 13, there was intraepidermal acantholysis, either suprabasal acantholysis with a tombstone aspect of the remaining basal cells and intact blister (in deep pemphigus cases, 6/13), or subcorneal acantholysis (in superficial ones, 5/13). One biopsy specimen revealed additional spongiosis with eosinophils (pemphigus herpetiformis), and one tissue specimen presented an ulcerated epidermis with numerous necrotized keratinocytes and dermal polymorphous inflammatory infiltrate (PAMS).

Direct immunofluorescence (DIF) was performed in nine cases, revealing intercellular deposition of IgG and C3 resembling a chicken wire in five cases and only IgG in three cases. In the case with PAMS, the DIF was negative.

Indirect immunofluorescence (IIF) revealed intercellular fluorescence in nine cases, and additional fluorescence along the dermo-epidermal junction was seen in one case (PAMS). IIF was negative in three cases.

Neither immunoblot nor enzyme-linked immunosorbent assay (ELISA) was performed because of their inaccessibility in Morocco.

Treatment

Eleven patients out of the thirteen received a high dose of oral prednisone as first-line therapy (2 mg/kg/day),

Table 1: Characteristics of the patients with pemphigus and associated malignancy at the Dermatology Department of Ibn Sina Hospital in Rabat.

Patient	1	2	3	4	5	6	7	8	9	10	11	12	13
Age (yrs.)/sex	68/F	49/F	67/M	59/F	80/M	56/M	55/M	81/F	45/M	53/F	64/F	56/F	70/M
Comorbidities	Hypertension Diabetes COVID-19	Angiocholitis	-	Diabetes Overweigh	Overweigh	-	Smoking Pulmonary hydatid cyst	Diabetes Pericarditis	-	Hypertension Epilepsy	Diabetes Hashimoto's thyroiditis	Hypertension Diabetes Moderate obesity Chronic urticaria	-
Clinical aspect	P vulgaris	P vegetans	P vulgaris + EM + PB	P vegetans	P vulgaris	P foliaceus	P vulgaris	P seborrheic	P herpetiformis	P vulgaris	P foliaceus	P seborrheic	P seborrheic
- Cutaneous lesions	+	+	+	+	+	+	+	+	+	+	+	+	+
- Mucosal lesions	B+G+A	B+N+A	O+B+N+G	G	B	-	B	-	B+G	G	-	-	-
- Pruritus	+	-	-	+	-	-	+	-		+	+	-	+
- PDAI	27	14	188	16	16	79	39	19	- 34	20	33	18	34
Histologic aspect	Intraepidermal suprabasal acantholysis and intact blister	Intraepidermal suprabasal acantholysis and papillomatous overlying epidermis	Ulcerated epidermis with numerous necrotized keratinocytes and dermal polymorphous inflammatory infiltrate	Intraepidermal suprabasal acantholysis and papillomatous overlying epidermis	Intraepidermal suprabasal acantholysis and intact blister	Intraepidermal subcorneal acantholysis	Intraepidermal suprabasal acantholysis and intact blister	Intraepidermal subcorneal acantholysis	Intraepidermal acantholysis + spongiosis with eosinophils	Intraepidermal suprabasal acantholysis and intact blister	Intraepidermal subcorneal acantholysis	Intraepidermal subcorneal acantholysis	Intraepidermal subcorneal acantholysis
DIF													
- IgG	Intercellular	Intercellular	-	Intercellular	Intercellular	NP	NP	Intercellular	NP	NP	Intercellular	Intercellular	Intercellular
- C3	Intercellular	-	-	Intercellular	Intercellular	NP	NP	Intercellular	NP	NP	-	Intercellular	-
IIF													
- Anti-intercellular substance antibodies	+ (1/1280)	+ (1/640)	+ (1/1280)	-	+ (1/320)	+ (1/1280)	+ (1/1280)	+ (1/80)	+ (1/20)	-	+ (1/120)	-	+ (1/320)
- Anti-basement membrane antibodies	-	-	+ (1/1280)	-	-	-	-	-	-	-	-	-	-
Associated cancer	Papillary thyroid carcinoma	Colon adenocarcinoma	B-cell chronic lymphocytic leukemia	3 squamous cell carcinoma (nail and skin) - Myelodysplasia - Concomitant with P	Prostate adenocarcinoma	Colon adenocarcinoma	Dermatofibrosarcoma protuberans	Papillary cystadenocarcinoma of the ovary	Squamous cell carcinoma of the palatin	Myelodysplasia	Breast adenocarcinoma	Papillary thyroid carcinoma	Neuroendocrine small bowel tumor
Time period to pemphigus onset	Concomitant with P	6 years after P	2 years before P	- 1 year before P	Concomitant with P	12 years before P	7 years after P	1 year after P	Concomitant with P	1 year before P	5 years before P	10 years after P	1 year before P

(Contd...)

Table 1: *(Continued).*

Patient	1	2	3	4	5	6	7	8	9	10	11	12	13
Treatment													
- Pemphigus	Oral prednisone (2mg/kg per day)	Oral prednisone (2mg/kg per day)	-	Oral prednisone (2mg/kg per day)	Oral prednisone (2mg/kg per day)	Oral prednisone (2mg/kg per day)	Oral prednisone (2mg/kg per day)	Oral prednisone (2mg/kg per day) + Oral Azathioprine (2mg/kg per day) Total hysterectomy and adnexectomy	Oral prednisone (2mg/kg per day)	Oral prednisone (2mg/kg per day)	Oral prednisone (2mg/kg per day)	Oral prednisone (2mg/kg per day)	Oral prednisone (2mg/kg per day)
- Cancer	Total thyroidectomy	Hemicolectomy	-	-Surgery with margins -Transfusion	Hormonal therapy	Hemicolectomy	Surgery with margins		Surgery with margins	Follow up	Tumorectomy + radiotherapy + hormonal therapy	Total thyroidectomy + iratherapy	Somatulin injection + small bowel resection
Evolution													
- Pemphigus	- Total healing after 90 days	- Total healing after 90 days, flare after 9 years	- Death after 3 weeks	Lost from follow-up	- Total healing after 180 days	- Total healing after 60 days, flare+ death after 12 years (sepsis)	- Total healing after 30 days, flare after 6 years	Total healing after 180 days, flare after 1 year	Lost from follow up	- Total healing after 45 days	- Total healing after 37 days	- Total healing after 37 days	- Total healing after 40 days
- Cancer	- Cured	- Cured			- Cured	- Cured	- Cured	- Cured		- Stabilized	- Cutaneous metastasis	- Cured	- Progression

F female, M male, P pemphigus, EM erythema multiform
O ocular B buccal N nasal G genital
NP not performed
PDAI pemphigus disease area index

one patient needed the adjunction of oral azathioprine (patient 8 at a dose of 2 mg/kg/day), and the case with PAMS died before treatment could be instituted.

Follow-up

Most patients (7/13) revealed complete healing of pemphigus lesions, after a mean time of 69.8 days. Four patients presented a pemphigus flare, after a mean period of six years with no cancer recurrence. Two patients were lost to follow-up. Two died (the patient with PAMS died three weeks after the onset of pemphigus from respiratory failure probably related to bronchiolitis obliterans).

Only two patients presented a progression of their cancer yet without a pemphigus flare.

DISCUSSION

The first cases of PPN published in the literature were highly severe and corresponded to diagnostic criteria defined by Anhalt et al. in 1990 [1]. These criteria have evolved to include atypical forms, such as cases without mucosal [2] or cutaneous involvement or detectable anti-plakin antibodies. They have been revised several times, in particular, by Camisa et al., Czernikc et al., Joly et al., and Grando et al. [6], without always specifying the number of criteria needed to establish the diagnosis. Therefore, the term *paraneoplastic autoimmune multiorgan syndrome* (PAMS) was proposed by Grando et al. in 2001 [3,4] to designate paraneoplastic disease with epithelial involvement, including PNP. The most consistently found criteria are severe mucosal involvement, polymorphic rash, acantholysis and lichenoid dermatitis in histopathology, and underlying neoplasia.

Our retrospective, descriptive study collected thirteen cases of pemphigus associated with cancer, in which only one case was classified to have PAMS (patient 3). He had a lymphoproliferative neoplasm occurring before the onset of pemphigus and developed polymorphous cutaneous manifestations with severe mucosal involvement. The autoantibodies directed against intercellular substance and basement membrane were present in IIF, and death occurred quickly after the onset of pemphigus from bronchiolitis obliterans.

Therefore, there appear to be cases of neoplasia fortuitously associated with classical pemphigus, and they have a better prognosis [6-12]. Joly et al. compared

34 cases of pemphigus associated with neoplasia, and only 22 were classified as cases of PNP (according to the PAMS criteria of classification) [6]. In our case series, 11 out of the 13 patients had a traditional form of pemphigus, 10 were moderately severe, and 7 presented complete healing of pemphigus lesions after a mean of 69.8 days without a flare. These findings highlight the better prognosis of these forms, in which there is an excellent therapeutic response and longer survival.

Only several studies have reported the relationship of pemphigus with neoplasia [13-16], and to the best of our knowledge, there is no data concerning this association in the Maghreb region. It is established in the literature that there is a statistically increased risk of solid malignancies in pemphigus. Ogawa et al. revealed in their study on 496 pemphigus cases that 5% developed an internal neoplasm, which was higher than in a group control of the same age (0.61%) [14]. Our findings were coherent with this data, as in our series on 302 cases of pemphigus, 4.3% had an associated neoplasm.

When a hematological malignancy was associated with pemphigus (patients 3, 4, and 10 in our case series), cancer developed before the onset of pemphigus. In all cases, there was a deep form of pemphigus, which is in accordance with the literature [14,15]. This result suggests that neoplasms triggered pemphigus, as in real paraneoplastic pemphigus. Schulze et al. reported the percentage of hematological malignancies in pemphigus vulgaris to be 3.9% vs. 0.23% in our series [15]. Lymphoproliferative malignancies were predominant, in contrast with our study. In our experience, there were mainly non-lymphoproliferative neoplasms among hematological malignancies, and they triggered the classical pemphigus type with moderate severity and good prognosis.

Regarding solid neoplasms, there is a statistically increased risk of oropharyngeal cancers (0.4% to 0.9%) [15,16], laryngeal cancer (0.6%) [15], and colon carcinomas (3.7% vs 0.15% in our case series) [15,16] in pemphigus vulgaris that have been established in the literature. However, there is no temporal relationship between pemphigus and internal malignancy, as in our series (patients 2 and 6 both with colon carcinoma). When mucosal cancer develops in pre-existing pemphigus, the chronic inflammation is responsible for genetic mutations and carcinogenesis, as in patient 2 with deep pemphigus and anal involvement, who developed colon carcinoma six years after pemphigus lesions. On the other hand, when mucosal cancer appears before pemphigus, it is stipulated that the neoplasm exposes specific antigens to the immune system, which triggers auto-immunity in pemphigus. However, patient 6, who had pre-existing colon carcinoma had a superficial pemphigus form with no mucosal involvement. This suggests that there might be other factors triggering both pemphigus and malignancy [17].

Concerning non-melanoma skin and mucosal cancers, we collected two cases of squamous cell carcinoma (patients 4 and 9) and one of sarcoma (patient 7), which corresponded to 0.23%. They all occurred in deep pemphigus types, again with no temporal relationship. This finding contrasts with the literature, in which non-melanoma skin cancers developed before the onset of pemphigus and were linked with pemphigus foliaceous in 16.5% of cases [15].

Our case series revealed that pemphigus immunosuppressive treatments did not trigger neoplasm as there is no temporal relationship between pemphigus and cancer occurrence, as in the literature [15,16]. And when cancer progresses, it is not followed by pemphigus recurrence (patients 2, 6, 7, and 8). This supports the hypothesis that there might be other factors involved in both pemphigus and cancer occurrence and is against a direct relationship between the two conditions [17].

At last, Kridin et al. demonstrated that comorbidity control did not significantly affect cancer incidence in pemphigus through statistical estimates [16]. In our series, comorbidities did not modify pemphigus response to therapeutics, and there were no malignancy-specific risk factors among comorbidities.

CONCLUSION

Our study had numerous limitations regarding the retrospective and monocentric analysis and the limited number of patients. However, our findings were coherent with the literature concerning an increased incidence of solid cancers in deep pemphigus subtypes without a temporal relationship. Patient comorbidities and pemphigus immunosuppressive treatments seemed not to be involved in the occurrence of malignancies. Regardless of the reason for this association, we should keep in mind a possible associated neoplasm in patients with deep pemphigus and perform a detailed examination for early diagnosis, although these cases seem to have a good prognosis. Further studies are still needed to characterize this association more fully.

Statement of Human and Animal Rights

All the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the 2008 revision of the Declaration of Helsinki of 1975.

Statement of Informed Consent

Informed consent for participation in this study was obtained from all patients.

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Source of Support: This article has no funding source.

Conflict of Interest: The authors have no conflict of interest to declare.