A systematic review of paraneoplastic pemphigus and paraneoplastic autoimmune multiorgan syndrome: Clinical features and prognostic factors

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Paraneoplastic pemphigus (PNP), also known as paraneoplastic autoimmune multiorgan syndrome (PAMS), is an autoimmune blistering disease that involves the skin, mucous membranes, and multiple organs, with a high mortality rate. However, due to the rarity of PNP/PAMS, there is a lack of large-scale studies, and its clinical features and prognostic factors are not fully understood. Thus, we conducted a search in four databases: PubMed, Web of Science, EMBASE, and Scopus, and identified 290 relevant articles (a total of 504 patients). Through analysis, we summarized the demographic information, clinical manifestations, histopathology, immunological characteristics, associated tumors, treatment medications, and their survival outcomes. After drawing the Kaplan-Meier survival curves for 281 patients with available survival information, it was found that older age, circulating bullous pemphigoid 230 autoantibodies, non-Hodgkin lymphoma, and possible history of causative drugs were associated with shorter survival time. Initial oral mucosal involvement, lichenoid/interface dermatitis, Castleman disease, and epithelial-derived tumors were associated with longer survival time. In the multifactorial Cox proportional hazards regression model, non-Hodgkin lymphoma (hazard ratio, 1.959; 95% CI, 1.286-2.985; $P = .002$) and lichenoid/interface dermatitis (hazard ratio, 0.555; 95% CI, 0.362-0.850; $P = .007$) remained associated with the prognosis of PNP/PAMS patients. (J Am Acad Dermatol 2025;92:307-10.)

Key words: paraneoplastic autoimmune multiorgan syndrome; paraneoplastic pemphigus; systematic review.

INTRODUCTION

It has been over 30 years since the first designation for paraneoplastic pemphigus (PNP) in 1990,[1] and in 2001, paraneoplastic autoimmune multiorgan syndrome (PAMS) was proposed to describe its characteristics of multiple organ involvement.[2] However, due to the rarity of the disease, there is a lack of large-scale research. Thus, we aimed to review all relevant cases, summarizing their characteristics and prognostic factors.

Abbreviations used:

PAMS: paraneoplastic autoimmune multiorgan syndrome
PNP: pemphigus pemphigus

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METHODS AND RESULTS

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines and the protocol was registered on the PROSPERO website (CRD42024540791). Paraneoplastic pemphigus and paraneoplastic autoimmune multiorgan syndrome were used as keywords to search on PubMed, Web of Science, EMBASE, and Scopus to find eligible literature from 1990 to April 2024. The diagnosis of PNP/PAMS was based on the S2k guideline in 2023.[3] Inclusion/exclusion criteria can be found in Supplementary Fig 1 (available via Mendeley at https://data.mendeley.com/datasets/cg98vy8krw/1). Statistical analyses were performed using SPSS (Version 23.0) and R software (Version 4.4.1).

Two researchers independently screened and reviewed the literature, including 290 articles (504 patients) (Supplementary Fig 1, available via Mendeley at https://data.mendeley.com/datasets/cg98vy8krw/1).

Patients were predominantly male (55.67%), with an average age of 48.27 years, and 69.85% of them initially presented with oral mucosal involvement (Table I). Acantholysis was the most common histological feature (65.61%), and antibody deposition was detectable by immunofluorescence in over 90% of patients (Supplementary Table I, available via Mendeley at https://data.mendeley.com/datasets/cg98vy8krw/1). Desmoglein 3 and envoplakin were the most frequent antigens (80.41%; 86.62%) in enzyme-linked immunosorbent assay and immunoblotting/immunoprecipitation, respectively (Supplementary Table II, available via Mendeley at https://data.mendeley.com/datasets/cg98vy8krw/1).

Non-Hodgkin lymphoma was the most common neoplasm (37.9%), followed by Castleman disease (28.57%) and neoplasms derived from epithelial tissues (19.25%), and more than half of the patients (54.51%) had dyspnea/respiratory failure (Supplementary Table III, available via Mendeley at https://data.mendeley.com/datasets/cg98vy8krw/1). Additionally, skin and mucosal lesions of 205 patients (60.29%) appeared before the diagnosis of neoplasms. The use of fludarabine was reported to possibly be related to the occurrence of PNP/PAMS in 16 patients (59.26%), while radiotherapy might be related to 14 cases (35.9%) (Supplementary Table IV, available via Mendeley at https://data.mendeley.com/datasets/cg98vy8krw/1).

217 deaths (56.51%) were reported, and respiratory failure was the most frequent cause (43.78%), followed by infection (24.88%) (Supplementary Table V, available via Mendeley at https://data.mendeley.com/datasets/cg98vy8krw/1). 281 patients were included in the drawing of Kaplan-Meier survival curves (Fig 1), and the median survival time was 24 months (95% confidence interval, 13.15-34.85). Through the log-rank test, older age (P = .0032), circulating bullous pemphigoid 230 autoantibodies (P = .0018), non-Hodgkin lymphoma (P < .0001), and possible history of causative drug (P = .0049) were associated with shorter survival time. Initial oral mucosal involvement (P = .0062), lichenoid/interface dermatitis (P = .0013), Castleman disease (P = .0007), and epithelial tissue neoplasm (P = .04) were associated with longer survival time. Variables above (excluding bullous pemphigoid 230 autoantibodies, due to sample size) were analyzed in Cox proportional hazards regression models, non-Hodgkin lymphoma (hazard ratio, 1.959; 95% confidence interval, 1.286-2.985; P = .002) and lichenoid/interface dermatitis

Table I. Clinical manifestations of PNP/PAMS patients

Manifestation	*n*	*N*	Percentage (%)
Sex			
Male	270	485	55.67
Female	215		44.33
Age	48.27 (mean)	_	20.72 (SD)
Male age	50.59 (mean)		19.62 (SD)
Female age	45.36 (mean)		21.72 (SD)
<18	68	482	14.11
18-60	247		51.24
≥60	167		34.65
Initial site			
Oral mucosa	227	325	69.85
Other mucosae	35		10.77
Skin	63		19.38
Mucosa involvement			
Oral	468	482	97.10
Pharynx/larynx	44		9.13
Eye	220		45.64
Nasal	19		3.94
Urinary/genital	196		40.66
Skin involvement			
Generalized	51	402	12.69
Extremity	151		37.56
Head/neck	41		10.20
Face	36		8.96
Trunk	194		48.26
Palmoplantar	88		21.89
Vesicle	203		50.50
Pustule	18		4.48
Erosion/ulcer	138		34.33
Erythema	140		34.83
Papule/plaque	127		31.59

PNP/PAMS, Paraneoplastic pemphigus/paraneoplastic autoimmune multiorgan syndrome; *SD*, standard deviation.

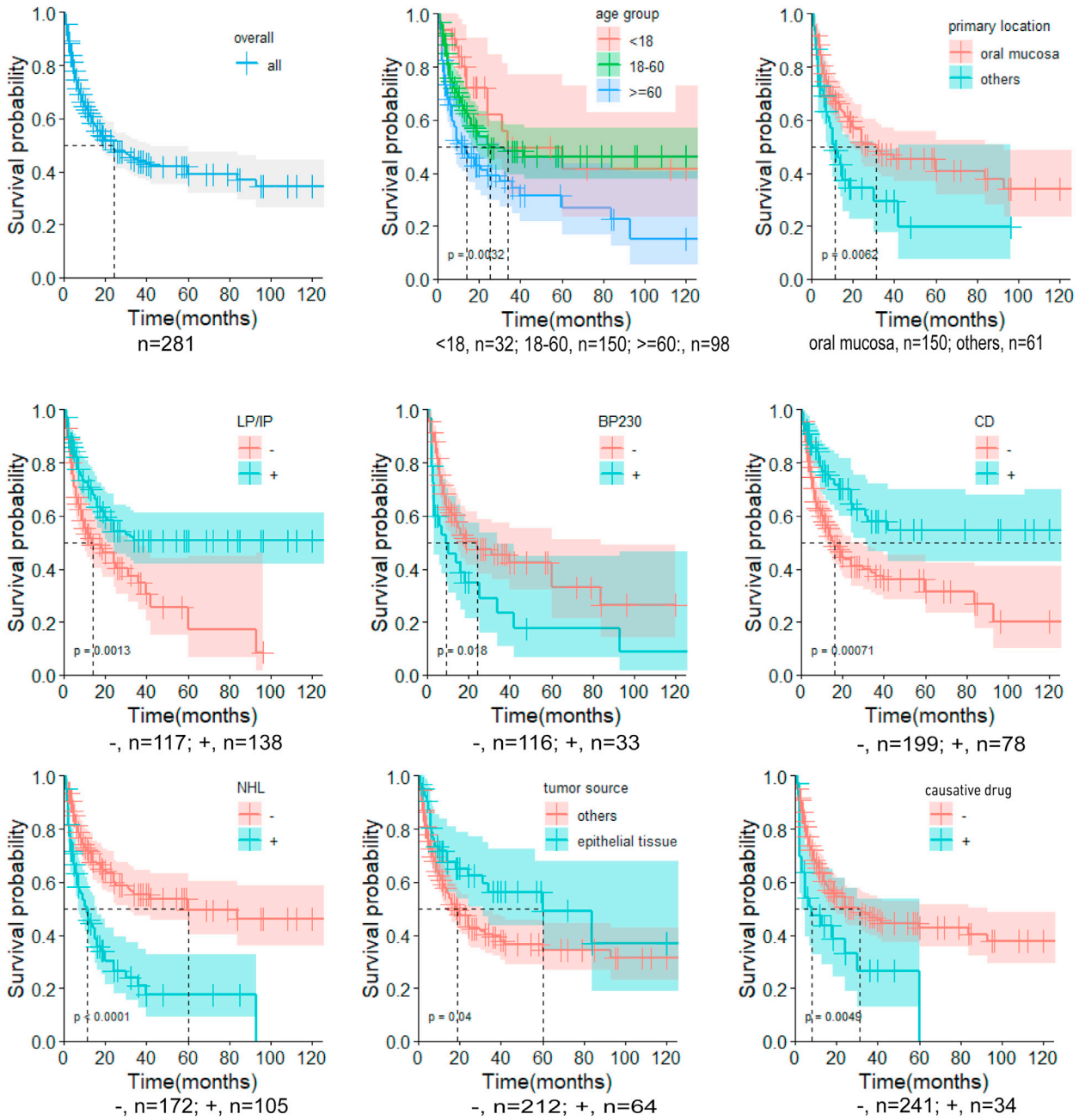

Fig 1. The Kaplan-Meier curves for patients with paraneoplastic pemphigus/paraneoplastic autoimmune multiorgan syndrome (PNP/PAMS). The starting point of time was when the patient presented with skin or mucosal symptoms of PNP/PAMS. Using the log-rank test to estimate *P* values and $P < .05$ is considered statistically significant. +, Yes/positive; -, no/negative; *BP*, bullous pemphigoid; *CD*, Castleman disease; *LP/IP*, lichenoid/interface dermatitis; *NHL*, non-Hodgkin lymphoma.

(hazard ratio, 0.555; 95% confidence interval, 0.362-0.850; $P = .007$) still remained significant.

CONCLUSION

To our knowledge, with the largest number of included literature and patients,[4,5] we systematically reviewed the characteristics of PNP/PAMS and found multiple factors were related to patient prognosis. The main limitation of the study is its reliance on case reports and case series, resulting in missing data and potential publication bias. Further prospective studies are necessary to confirm these findings.

Conflicts of interest

None disclosed.

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JAAD Game changer

JAAD Game Changers: The use of oral antibiotics before isotretinoin therapy in patients with acne

Adam Friedman, MD

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How did this article change the practice of dermatology?

- Oral antibiotics have been the mainstay of acne treatment for decades, but all good things come with a price (cough and antimicrobial resistance).
- Although efforts have been made to curtail the excessive use of antibiotic-active dosing of these drugs, investigators herein demonstrate that the lights are on but nobody is home.
- This study serves as a call to action to better educate our peers and patients about proper and meaningful antibiotic use in order to prevent the selection of drug-resistant organisms and chronic disruption of our cutaneous and gut microbiota.

Conflicts of interest: None disclosed.

Note: A Game Changer is a short narrative stating how an article that originally appeared in *JAAD* changed the game of dermatology. The Game Changer author is not the author of the original article.

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