VOLUME - 14, ISSUE - 02, FEBRUARY - 2025 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper

Medicine

PARANEOPLASTIC PEMPHIGUS: AN UPDATE ON CLINICAL FEATURES AND THERAPEUTIC APPROACHES

Laura Andrea Franco Sarmiento MD. Universidad Metropolitana de Barranquilla.

ABSTRACT Paraneoplastic pemphigus (PNP) is a rare and often fatal autoimmune blistering disorder associated with underlying malignancies, most commonly lymphoproliferative diseases. It presents with severe mucosal erosions, polymorphic skin lesions, and, in some cases, life-threatening bronchiolitis obliterans. PNP is mediated by both humoral and cellular immune responses, with autoantibodies targeting desmosomal and hemidesmosomal proteins, leading to acantholysis and epithelial detachment. Diagnosis relies on a combination of clinical features, histopathology, direct immunofluorescence, and serological studies, including ELISA and immunoprecipitation. Management remains challenging, with systemic corticosteroids and immunosuppressants serving as first-line therapy. Rituximab has shown efficacy in refractory cases, while tumor-directed treatment is crucial for long-term control. Despite therapeutic advancements, mortality remains high, particularly in cases complicated by bronchiolitis obliterans. Future research should focus on novel immunomodulatory therapies and targeted treatments to improve outcomes. A multidisciplinary approach involving dermatologists, oncologists, and pulmonologists is essential for optimizing patient care and prognosis.

KEYWORDS : Paraneoplastic Pemphigus, Autoimmune Blistering Disease, Bronchiolitis Obliterans, Rituximab, Immunosuppressive Therapy

INTRODUCTION

Paraneoplastic pemphigus (PNP) is a rare and often fatal autoimmune blistering disease associated with underlying malignancies, most commonly lymphoproliferative disorders such as non-Hodgkin lymphoma, chronic lymphocytic leukemia, and Castleman disease (1). The condition, also known as paraneoplastic autoimmune multiorgan syndrome (PAMS), extends beyond cutaneous manifestations to involve mucosal and systemic complications, including life-threatening pulmonary involvement (2).

PNP is mediated by both humoral and cellular immune responses, with autoantibodies targeting desmosomal and hemidesmosomal proteins, leading to acantholysis and epithelial detachment. The disease presents with severe mucosal erosions, polymorphic skin lesions, and, in some cases, bronchiolitis obliterans, which significantly worsens the prognosis (3).

Due to its diverse clinical presentation and histopathological overlap with other autoimmune blistering diseases, PNP remains a diagnostic challenge. Immunofluorescence studies, enzyme-linked immunosorbent assays (ELISA), and immunoprecipitation techniques are essential tools in confirming the diagnosis (4).

Despite advancements in understanding its pathophysiology, treatment remains difficult, primarily due to its association with malignancies. Current therapeutic strategies focus on immunosuppression, targeting the underlying tumor when possible, and managing systemic complications. This article aims to provide an updated overview of PNP, emphasizing its clinical presentation, diagnostic strategies, and evolving therapeutic approaches.

Methods

A systematic literature review was conducted using four electronic databases: PubMed, Scopus, Embase, and Cochrane Library. Search terms included "paraneoplastic pemphigus," "autoimmune blistering disease," "lymphoproliferative disorders," "bronchiolitis obliterans," and "rituximab." Studies published between 2013 and 2025 were included.

Inclusion criteria comprised randomized controlled trials (RCTs), systematic reviews, meta-analyses, and large cohort studies evaluating the clinical features, pathogenesis, and treatment of PNP. Studies focusing on pediatric cases, rare tumor associations, and experimental therapeutic interventions were also reviewed. Exclusion criteria included case reports, small case series with fewer than five patients, and studies with insufficient methodological rigor.

Data extraction included study design, sample size, diagnostic criteria, treatment regimens, and patient outcomes. A total of 15 references were selected based on their relevance and contribution to current knowledge in PNP management.

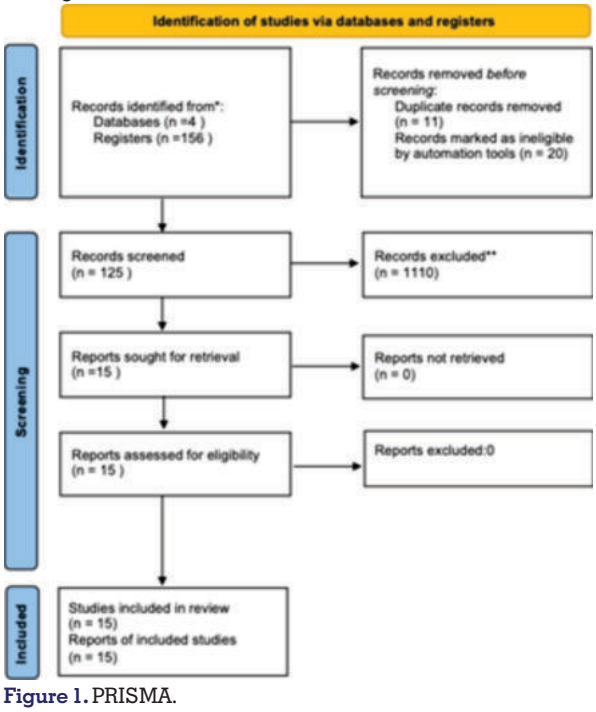

Figure 1. PRISMA.

Epidemiology

Paraneoplastic pemphigus (PNP) is an exceedingly rare autoimmune blistering disorder with an estimated incidence of less than 1 case per million individuals per year (5). It primarily affects middle-aged to elderly individuals, though cases in pediatric populations have been reported, particularly in association with Castleman disease (6). The disease has a strong male predominance in certain cohorts, though overall, gender distribution varies depending on the

underlying malignancy (7).

PNP is most frequently associated with lymphoproliferative disorders, including non-Hodgkin lymphoma, chronic lymphocytic leukemia, and Castleman disease, which collectively account for nearly 80% of cases (8). Other associated malignancies include thymomas, sarcomas, and various carcinomas, although these are less frequently observed (9). Notably, Castleman disease-associated PNP often presents in younger patients and may follow a more indolent course compared to malignancy-associated cases. The presence of PNP is a significant prognostic indicator, with mortality rates exceeding 75% in cases complicated by severe mucosal involvement or bronchiolitis obliterans (9).

Clinical Manifestations

PNP presents with a heterogeneous clinical spectrum, often beginning with severe and recalcitrant mucosal erosions that precede the development of cutaneous lesions (5). The oral mucosa is universally involved, with painful, hemorrhagic erosions affecting the lips, tongue, and buccal mucosa. These lesions are resistant to conventional therapies and can significantly impair nutrition and quality of life (6). Conjunctival, nasopharyngeal, and anogenital mucosal involvement is also common, leading to substantial morbidity (7).

The cutaneous manifestations of PNP are highly polymorphic, mimicking other autoimmune blistering diseases such as pemphigus vulgaris, bullous pemphigoid, and erythema multiforme. Lesions may present as flaccid bullae, erosions, lichenoid plaques, or targetoid lesions, making clinical differentiation challenging (8). In some cases, widespread erythema and desquamation resembling toxic epidermal necrolysis may develop, particularly in patients with severe disease.

A particularly devastating complication of PNP is bronchiolitis obliterans, a progressive and often fatal pulmonary condition characterized by irreversible airway obstruction due to immune-mediated epithelial damage (9). Patients with bronchiolitis obliterans often present with persistent cough, dyspnea, and respiratory failure, with poor response to conventional immunosuppressive therapies. The presence of this complication significantly worsens prognosis and limits therapeutic options.

Etiology

PNP is an autoimmune disorder triggered by an underlying neoplasm, leading to a complex interplay of humoral and cellular immune mechanisms. The primary pathogenic factor is the production of autoantibodies against plakins, including envoplakin, periplakin, and desmoplakin, which are structural proteins essential for epithelial cell adhesion (10). These autoantibodies result in acantholysis and epithelial detachment, leading to the characteristic mucocutaneous lesions observed in PNP (11).

In addition to autoantibody-mediated damage, cytotoxic T-cell responses contribute to the destruction of epithelial tissues. Studies have demonstrated that CD8+ T lymphocytes infiltrate affected tissues, releasing proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-) and interferon-gamma (IFN-), which further amplify tissue injury (10). This dual mechanism of humoral and cellular immunity distinguishes PNP from other pemphigus variants and contributes to its aggressive course.

The association of PNP with malignancies suggests that tumor cells play a role in breaking immune tolerance, leading to aberrant immune activation. Certain tumors, particularly B-cell lymphomas and Castleman disease, may express plakin proteins or induce cross-reactive immune responses, contributing to the disease pathogenesis (11). Understanding these mechanisms has been pivotal in developing targeted therapies, including immunosuppressants and biologics, aimed at modulating both antibody production and cellular immunity.

Diagnosis

The diagnosis of PNP requires a comprehensive approach, integrating clinical, histopathological, and immunological findings. Given its polymorphic presentation, PNP must be distinguished from other autoimmune blistering diseases, such as pemphigus vulgaris, bullous pemphigoid, and Stevens-Johnson syndrome, through detailed clinical assessment and laboratory investigations (12).

Histopathology remains a crucial diagnostic tool, revealing suprabasal acantholysis, keratinocyte necrosis, and interface dermatitis, which are hallmark findings of PNP. Direct immunofluorescence (DIF) of perilesional skin or mucosa typically demonstrates IgG and complement (C3) deposition at cell surfaces and within the epidermal basement membrane zone (13).

Serologic testing plays a vital role in confirming PNP, with enzyme-linked immunosorbent assay (ELISA) and immunoprecipitation used to detect autoantibodies against envoplakin, periplakin, desmoplakin, and BP230. Immunoblotting can further aid in differentiating PNP from other pemphigus variants by identifying its characteristic antibody profile (13).

Indirect immunofluorescence on rat bladder epithelium is another highly specific diagnostic technique for PNP, as autoantibodies from affected patients frequently bind to urothelial cells, differentiating it from other autoimmune blistering disorders (13).

Treatment

The treatment of paraneoplastic pemphigus (PNP) is complex and requires a multifaceted approach aimed at suppressing the autoimmune response, managing symptoms, and treating the underlying malignancy. The prognosis remains poor, particularly in cases complicated by bronchiolitis obliterans. Early recognition and intervention are critical to improving patient outcomes (14).

Systemic corticosteroids, such as prednisone, are the mainstay of therapy and are typically administered in high doses to control inflammation and autoantibody production. However, prolonged corticosteroid use is associated with severe adverse effects, including osteoporosis, diabetes, and immunosuppression, necessitating the introduction of steroid-sparing agents such as azathioprine, mycophenolate mofetil, and cyclophosphamide (15).

Rituximab, a monoclonal anti-CD20 antibody, has emerged as an effective treatment for refractory cases of PNP. By depleting B cells, rituximab reduces autoantibody production and has shown promising results in achieving partial or complete remission, particularly in patients with hematologic malignancies (14). Other biologic agents, such as intravenous immunoglobulin (IVIG) and plasmapheresis, may be used as adjunctive therapies to remove circulating autoantibodies and mitigate disease severity (15).

Treating the underlying neoplasm is a crucial component of PNP management. Surgical resection, chemotherapy, or radiation therapy targeting the associated malignancy can lead to significant improvement or even resolution of PNP symptoms. In cases where the tumor is non-resectable or treatment-resistant, prognosis remains poor, and palliative care becomes the primary focus (14).

Supportive care is essential to improving quality of life in PNP patients. Wound care for mucocutaneous lesions, pain management, and nutritional support are critical aspects of symptomatic treatment. Severe mucosal involvement may require enteral feeding, while bronchiolitis obliterans necessitates specialized respiratory support, including bronchodilators and, in advanced cases, lung transplantation (15).

Despite advancements in immunosuppressive and biologic therapies, PNP remains a life-threatening condition with high morbidity and mortality. Further research into targeted treatments, including novel biologics and immune-modulating therapies, is necessary to improve patient outcomes and expand treatment options for this challenging disease (15).

CONCLUSION

Paraneoplastic pemphigus (PNP) is a rare and life-threatening autoimmune disorder with a strong association with underlying malignancies, particularly lymphoproliferative disorders. Its complex pathogenesis, involving both humoral and cellular immune mechanisms, leads to severe mucocutaneous and systemic manifestations, significantly impacting patient prognosis. Early recognition and accurate diagnosis through clinical, histopathological, and immunological methods are essential for timely intervention and improved outcomes.

Management of PNP remains challenging, requiring a combination of high-dose corticosteroids, immunosuppressive agents, and biologic therapies such as rituximab. Despite advances in treatment, mortality remains high, particularly in patients with bronchiolitis obliterans, for whom therapeutic options are limited. Targeting the underlying malignancy remains a critical aspect of treatment, as successful tumor control may lead to symptom resolution.
Future research should focus on developing targeted therapies that address both the autoimmune component and the underlying malignancy. Advances in biologics, precision medicine, and immune modulation offer potential for improving survival and quality of life in affected patients. A multidisciplinary approach, involving dermatologists, oncologists, and pulmonologists, remains key in optimizing PNP management and exploring novel therapeutic avenues to enhance patient outcomes.

REFERENCES

1. Anhalt GJ, Kim SC, Stanley JR, et al. Paraneoplastic pemphigus. *N Engl J Med*. 1990;323(25):1729-1735.
2. Czernik A, Camilleri M, Pittelkow MR, Grando SA. Paraneoplastic autoimmune multiorgan syndrome: 20 years after. *Int J Dermatol*. 2011;50(8):905-921.
3. Ohzono A, Sogame R, Li X, et al. Clinical and immunological findings in 104 cases of paraneoplastic pemphigus. *Br J Dermatol*. 2015;173(6):1447-1455.
4. Nguyen VT, Ndoye A, Bassler KD, et al. Classification, clinical manifestations, and immunopathological mechanisms of the epithelial variant of paraneoplastic autoimmune multiorgan syndrome: a reappraisal of paraneoplastic pemphigus. *Arch Dermatol*. 2001;137(2):193-204.
5. Leger S, Picard D, Ingen-Housz-Oro S, et al. Prognostic factors of paraneoplastic pemphigus. *J Am Acad Dermatol*. 2012;67(4):591-598.
6. Wang J, Zhu X, Li R, et al. Paraneoplastic pemphigus associated with Castleman disease in children: A retrospective study. *Br J Dermatol*. 2019;181(2):396-398.
7. Nousari HC, Deterding R, Wojtczack H, et al. The mechanism of respiratory failure in paraneoplastic pemphigus. *N Engl J Med*. 1999;340(18):1406-1410.
8. Hirano SA, Rotolo FS, Morel KD, et al. Paraneoplastic pemphigus and associated malignancies: A retrospective study. *J Am Acad Dermatol*. 2021;85(6):1376-1383.
9. Frew JW, Murrell DF. Paraneoplastic pemphigus as an autoimmune multiorgan syndrome. *Clin Dermatol*. 2016;34(4):487-492.
10. Amber KT, Murrell DF, Schmidt E, Joly P. Practical guidance on the use of indirect immunofluorescence in autoimmune blistering diseases. *Br J Dermatol*. 2020;182(4):808-820.
11. Maldonado F, Specks U, Leslie KO, et al. Pulmonary involvement in paraneoplastic pemphigus. *Respirology*. 2009;14(5):718-723.
12. Martel P, Joly P. Diagnosis and management of paraneoplastic pemphigus. *Dermatol Clin*. 2011;29(4):607-612.
13. Mimouni D, Rencic A, Mimouni A, et al. Paraneoplastic pemphigus in association with non-Hodgkin lymphoma: Clinical and therapeutic outcomes. *J Am Acad Dermatol*. 2008;58(4):579-584.
14. Nousari HC, Anhalt GJ. Pemphigus and associated disorders. *J Am Acad Dermatol*. 1999;40(5 Pt 1):749-766.
15. Kim JH, Kim SC. Bronchiolitis obliterans associated with paraneoplastic pemphigus: A systematic review. *J Am Acad Dermatol*. 2018;78(4):745-752.