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REVIEW ARTICLE

Paraneoplastic pemphigus: A *trait d'union* between dermatology and oncology

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***Abstract*:** Paraneoplastic pemphigus is a rare autoimmune disease of the skin associated with neoplasm. Nowadays, the pathogenesis of paraneoplastic pemphigus is not fully understood. Due to its rarity, various criteria have been proposed for the diagnosis. For this reason, several diagnostic methods have been considered useful for the diagnosis of paraneoplastic pemphigus including indirect immunofluorescence, direct immune of fluorescence, immunoprecipitation, immunoblotting, and enzyme-linked immunosorbent assay (ELISA). However, the polymorphic clinical features and the various results of laboratory tests and pathological evaluation present a challenge for the clinicians.

Keywords: paraneoplastic pemphigus; oncology; cancer; therapy

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Paraneoplastic pemphigus (PNP) is a rare autoimmune blistering disease of the skin, which was first described by Anhalt et al. in 1990[1]. PNP is always associated with neoplasm, among which B-cell lymphomas and other hematological malignant diseases are most common[2]. In 2001, Nguyen et al. suggested the term "paraneoplastic autoimmune multiorgan syndrome" (PAMS) as several organs are affected and autoantibodies bind several tissues[3]. Due to its high mortality rate, PNP must be detected quickly[4].

Epidemiology

PNP is a rare disease. Presently, there is limited data on the prevalence of PNP. Over 450 cases are described in the literature to date[5,6]. PNP usually affects patients aged between 45 and 70 years. Ogawa et al. reported that the mean age of onset in his series was 64.7[7]. However, PNP can affect every age group, including children and adolescents[8-10]. PNP appears to affect males and females equally[2].

Etiology

PNP is mostly associated with lymphoproliferative disorders[2]. Nearly 84% of all PNP are found in association with hematologic neoplasms or disorders[2,6]. Among these, non-Hodgkin's lymphoma accounts for 38.6%, chronic lymphocytic leukemia for 18.4%, Castleman's disease for 18.4%, thymoma for 5.5%, Waldenstrom's macroglobulinemia for 1.2%, Hodgkin's lymphoma for 0.6%, and monoclonal gammopathy for 0.6%[2,5,6,11]. In addition, carcinomas developed from epithelial cells (8.6%)[12-14], sarcomas derived from mesenchymal lines (6.2%)[9,15,16], and melanoma (0.6%)[17] also are reported in association with PNP. There are also cases of PNP triggered by cytotoxic drugs[18,19] and radiotherapy[20] described in the literature.

Genetics

HLA-DRB1*03 and HLA-Cw*14 are associated with PNP in Caucasian[21] and in Chinese patients[22] respectively. The HLA-DRB1*03 and the HLA-Cw*14 alleles were found more frequently, respectively in a series of 13 Caucasian French patients[21] and of 19 Han Chinese patients[22] than in the control populations. The Chinese patients with PNP did not show HLA-DRB1*03 allele[22].

Pathogenesis

The pathogenesis of PNP is not completely known. On one hand, several autoantibodies could play a pivotal role in PNP. Autoantibodies directed against the plakin family are typically found in PNP, including antibodies against the 210 kDa envoplakin, the 190 kDa periplakin, the 250 and 210 kDa desmoplakins I and II, the 500 kDa plectin, and the 230 kDa bullous pemphigoid antigen[23-26]. Furthermore, antibodies against plakophilin 3 and desmocollins (DSC) 1–3 have also been detected in some studies[27,28]. In addition, autoantibodies against desmoglein-1 (DSG-1) and desmoglein-3 (DSG-3) may also have pathogenic activity[29,30]. However, Amagai et al. reported a positivity of 100% only for anti-DSG-3 autoantibodies[29]. Recently, the protease inhibitor α2-macroglobulin-like-1 (A2ML1) has been considered as the possible pathogenic in PNP[31,32].

On the other hand, the cell-mediated immunity could have a role in PNP[2,33]. Another study reported the presence of selective epidermal activated CD8+ T-cells in PNP[34]. There are also four PNP patients without any detectable autoantibodies described by Cummins et al[35]. Furthermore, another study showed that MHC-restricted CD8+ cytotoxic T lymphocytes, non-MHC-restricted CD56+, and CD68+ natural killer cells are at the dermo-epidermal junction of PNP lesions[36].

Clinical features

PNP is identified by polymorphous lesions involving the skin and different mucosae. The variety of lesions could be explained by the presence of different autoantibodies in different patients[2]. Mucosal lesions are often the earliest features in PNP[37-39]. Oral mucosa is always affected in PNP (*Figure 1*)[37-40], although one PNP case without oral involvement is reported in the literature[41]. Usually severe erosions and crusting are found on the vermilion of the lips, showing an erythema multiforme-like or a Stevens-Johnson-like appearance. Erosions also affect the oropharynx, causing a painful stomatitis. In addition, mucosal lesion can also involve the nasopharynx, conjunctivae, anogenital region, and esophagus[6,42,43]. Cutaneous lesions usually rise after the onset of mucosal lesions[2,40]. The most involved sites are the trunk, head, neck, and proximal extremities, although most patients show a widespread cutaneous involvement (*Figure 2*)[4,40,44]. Different kind of lesions may coexist and evolve from one type to another[3,40]. Cutaneous lesions could be similar to those seen in pemphigus, pemphigoid, erythema multiforme or graft versus host disease[11,38,40]. Pustular and psoriasis form presentation have also been described[3]. The different clinical features could be linked to the predominance of the cell-mediated or humoral-mediated cytotoxicity[36,38]. It is well known that if the principal mechanism is humoral-mediated cytotoxicity, a usual pemphigus appearance might be prominent[3,6]. In contrast, if cell-mediated cytotoxicity is the leading mechanism, lichenoid lesions might be easily seen[33,35,36]. Lichenoid lesions are commonly detected in children, especially on the trunk and limbs[9,10]. Lesions resembling those of pemphigoid are usually present on the extremities[45]. Sapadin et al. reported a singular case of pemphigus vegetans-like

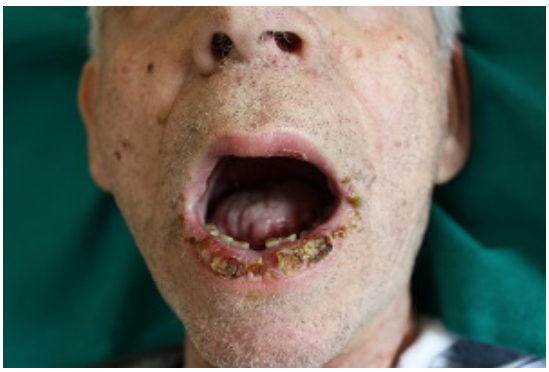

Figure 1 Painful erosions of the lips

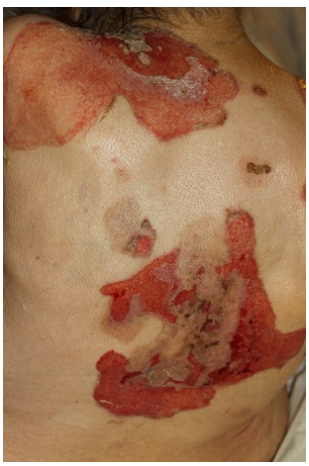

Figure 2 Extensive areas of denudation

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PNP[46]. PNP can also involve the respiratory epithelium in 59.1%–92.8% of cases[8,36], causing dyspnea, obstructive lung disease and bronchiolitis obliterans, which may be fatal[6,47]. However, the pulmonary involvement affects mainly children and Chinese patients with Castleman's disease[40,47]. Usually, a neoplasm is detected before the onset of PNP[4,38–40]. However, in about 30% of cases PNP, the clinical manifestation leads to the detection of an occult tumor[36,38].

Histological features

The pathological findings vary with the clinical features[4,30]. On one hand, suprabasal acantholysis with scattered inflammatory infiltrates could be detected in presence of blisters (*Figure 3*)[30]. Furthermore, the presence of dyskeratosis with suprabasal acantholysis is a clue to paraneoplastic pemphigus. On the other hand, interface and lichenoid dermatitis are more easily detected in erythematous inflammatory maculopapular lesions[30,35]. Lesions with a mixed clinical feature might show concomitant acantholysis occurring with lichenoid interface dermatitis[30,38,40].

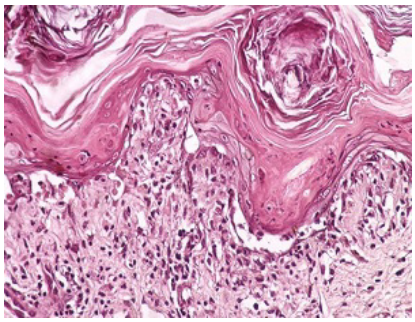

Figure 3 Histology of a skin biopsy shows suprabasal acantholysis. (H&E, magnification 200×)

Immunological studies

Direct immunofluorescence (DIF) usually shows IgG and/or C3 deposition in the epidermal intercellular spaces (EIS) alone[48]. The deposition of IgG and/or C3 in EIS and in the basement membrane zone is reported to be less than 50% of cases[48]. In addition, linear deposits of IgG or C3 in the basement membrane zone could be detected[30]. This pattern could be a clue to differentiate PNP from other forms of pemphigus, in which Ig deposits are detected only between keratinocytes[3]. However, DIF is found to be negative in approximately 50% of the cases[48]. False negatives are commonly due to necrotic tissue (especially in mucosal biopsies) and the lichenoid clinical pattern of some lesions[35,48].

Indirect immunofluorescence (IIF) could be performed on different substrates, including normal human skin, rat bladder (*Figure 4*), rat myocardium, rat lung, and monkey esophagus[48]. IIF detects autoantibodies to plakins; among them, autoantibodies to envoplakin and periplakin are the most specific[30]. IIF on normal human skin has been shown to be positive in up to 50% of the cases, whereas IIF on rat bladder urothelium has been found positive in 75% of the cases, showing a better sensitivity[38,49]. Furthermore, IIF on rat bladder has shown a high specificity (83%)[1,49]. For these reasons, IIF on rat bladder is now considered a useful screening test for PNP. However, autoantibodies directed against members of plakin family have been also detected in other conditions including pemphigus vulgaris, pemphigus foliaceus and Lyell's syndrome[49-51].

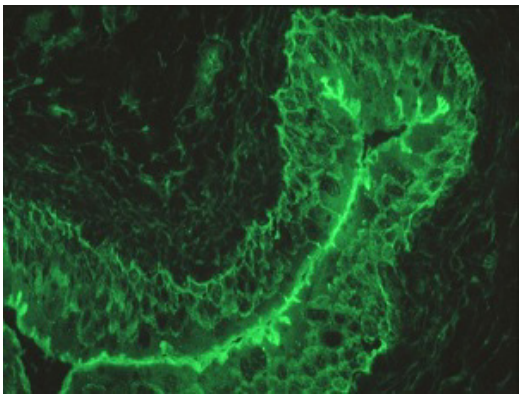

Figure 4 Positive indirect immunofluorescence on rat urinary bladder epithelium

Enzyme-linked immunosorbent assay (ELISA) can be used to detect anti-DSG-3 and anti-DSG-1 autoantibodies in PNP, although most PNP patients have been shown only with anti-DSG-3 IgG[52]. However, there were also PNP patients without anti-DSG autoantibodies described in the literature[52]. In 2009, Probst et al. developed a new ELISA using a recombinant 56 kDa N-terminal fragment of envoplakin which shows a sensitivity of 82% and a specificity of ≥ 98%[53]. Recently, Ishii et al. detected IgG autoantibodies to DSC-1, DSC-2 and DSC-3 in 16.5%, 36.7% and 59.5% of PNP sera respectively, using a novel mammalian ELISA[54].

Immunoprecipitation (IP) has been considered as the gold standard for the diagnosis of PNP[55]. IP can show antibodies against several epidermal antigens, including plakin family and A2ML1[31]. In addition, a positive IP test is a major criterion for the diagnosis of PNP[56].

Immunoblotting (IB) has been used to detect antibodies against desmoplakin I and II, periplakin, and envoplakin on normal human keratinocytes extracts[30,48].

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Diagnosis

According to Anhalt et al., the diagnostic criteria includes five different points (*Table 1*)[1]. However, Camisa et al. proposed different criteria, including major and minor criteria (*Table 2*)[56]. According to Camisa et al., three major criteria or two major and two minor criteria are needed to diagnose PNP[56]. Furthermore, Mimouni et al.[9] revised the original criteria proposed by Anhalt et al.[1] (*Table 3*). Nowadays, DIF is considered non-essential for diagnosing PNP due to its low sensibility[48,49]. IIF on rat bladder urothelium and monkey esophagus are thought to be useful as a screening for PNP[36,38,48]. In addition, the detection of anti-DSG-3, anti-DSG-1, anti-DSC-1, anti-DSC-2 and anti-DSC-3 antibodies by ELISA is useful to formulate a correct diagnosis[57]. Furthermore, the link between anti-DSG-3 antibodies and bronchiolitis obliterans (BO)[58] has been reported as one of the most important complications of PNP patients. The detection of antibodies against A2ML1 using IP and IB is also useful for the diagnosis of PNP[31,57]. Indeed, Ohzono et al. reported that 60.4% of the patients showed positivity for anti-A2ML1 antibodies that was higher than the positivity for anti-DSG-1 antibodies[57].

In conclusion, as PNP is primarily associated with antibodies against the plakin family, IP is considered as the laboratory gold standard for the diagnosis of PNP[55,56]. However, rat bladder IIF in combination with IB offers an easier and more accurate alternative to IP[59]. Furthermore, the laboratory data should be related to the clinical features[38-40]. In addition, it is mandatory to detect the underlying malignancy[38-40].

Table 1 Diagnostic criteria originally proposed by Anhalt et al.[1]

Parameter	Criterion
Clinical features	Painful erosions involving mucosae with or without a multiform skin eruption producing blisters and erosions, occurring in association with an occult or evident neoplasm
Histopathology	Suprabasal intraepithelial acantholysis, vacuolar interface changes and necrosis of individual keratinocytes
Direct immunofluorescence	Combined presence of IgG and complement (C3) granular-linear deposition within the epidermal intercellular spaces and along the basement-membrane zone
Indirect immunofluorescence	Presence of circulating antibodies that target the intercellular zone of stratified squamous or transitional epithelia
Immunoprecipitation	Typical complex of proteins including desmoplakin I (250 kD), bullous pemphigoid antigen (230 kD), envoplakin (210 kD), desmoplakin II (210 kD), periplakin (190 kD) and α-2-macroglobulin-like-1 (170kD)

Table 2 Diagnostic criteria proposed by Camisa et al.[55]

Relevance	Description
Major	Polymorphic clinical features involving the skin and mucosae
	Presence of an underlying neoplasia
	Characteristic immunoprecipitation pattern of auto-antibodies
Minor	Clear acantholysis on skin biopsy
	Direct immunofluorescence highlighting intercellular and basement membrane staining
	Positive indirect immunofluorescence on rat-bladder epithelium

Table 3 Diagnostic criteria proposed by Mimouni et al.[9]

Criterion
Detection of auto-antibodies against desmoglein 1 and 3, envoplakin, periplakin, and plectin
Exclusion of other disease positive to anti-desmoglein 1 and 3 autoantibodies
Respiratory tract affected by the disease
Lichenoid clinical features on skin

Treatment options

High-dose corticosteroids are used as the first line therapy[60,61]. However, corticosteroids are usually combined with other immunosuppressive drugs. Only two papers reported an improvement of the lesions using only corticosteroids[60,61]. Prednisolone in association with other immunosuppressive drugs including azathioprine[1], cyclosporine[62], mycophenolate mofetil[63] and cyclophosphamide[64,65] have been shown efficient. In addition, the combination of prednisolone and intravenous immunoglobulins[38-40] or plasmapheresis[66,67] have been reported effective in selected number of patients. However, mucosal lesions are usually resistant to most of the therapeutic schedules.

Rituximab, the anti-CD20 monoclonal antibody, has improved the clinical picture in PNP patients with underlying B-cell lymphoma[11,68,69]. Alemtuzumab, a humanized monoclonal antibody which binds CD52, has induced a long-term remission in a patient with B-cell chronic lymphocytic leukemia[70]. Daclizumab, a humanized monoclonal antibody directed against the alpha subunit of the IL-2 receptor of T-cells, is found to be a promising drug in treating PNP[38].

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On the other hand, whenever feasible, a complete excision of the benign tumor should be performed. This may cause an important improvement of the clinical picture due to a dramatic reduction of autoantibodies[11,38-40]. It has also been suggested to use perioperative intravenous immunoglobulins to block the release of autoantibodies during excision[11]. On the contrary, there is no consensus regarding the management of a malignant tumor as, in some cases, PNP continues to develop despite surgery and chemotherapy[11,38-40].

Early antimicrobial therapy is recommended to reduce the risk of sepsis due to loss of skin integrity and immunosuppressive therapy[11]. Antalgic therapy is thought to be useful in reducing the pain linked to extensive mucosal erosions[11].

Prognosis

The prognosis of PNP is generally poor, with a staggering 90% mortality rate[4-6,11]. The death is usually caused by severe complications including sepsis, gastrointestinal bleedings and BO[4-6,11]. At this regard, a link between anti-DSG-3 antibodies and BO has been reported[58]. Thus, it is important to evaluate accurately the respiratory symptoms in patients with a positivity to anti-DSG-3 antibodies.

PNP and underlying malignancy do not have a parallel evolution[4-6]. In fact, PNP lesions generally progress even if malignancy is removed or under controlled[8-11]. However, it has been highlighted that the outcome is better in PNP patients with concurrent Castleman's disease or benign thymomas upon removal of the tumor[71]. Nevertheless, Dong et al. emphasized that PNP was an independent detrimental prognostic factor in Castleman's disease patients which affects the survival rate of these patients[72].

Conclusion

Due to its polymorphus clinical appearance, PNP presents a challenge for the clinicians. Although several immunological makers have been discovered, the pathogenesis remains largely unknown. Different therapies have been developed to treat this severe condition as the management of the underlying tumor is vital.

Conflict of interest

The authors declared no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

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