

## Review

# Paraneoplastic autoimmune multi-organ syndrome and oral mucosa involvement: an intriguing disorder

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## Abstract

Paraneoplastic autoimmune multi-organ syndrome (PAMS) is a life threatening autoimmune disease almost always associated with neoplasia. Patients with this rare disorder present severe blistering and painful erosions of the oral cavity and may exhibit one of a spectrum of at least five clinical variants of the mucocutaneous disease such as pemphigus like, pemphigoid-like, erythema multiforme-like, graft-versus-host disease-like, and lichen planus-like. This syndrome involves multiple organ systems, and its high mortality rate frequently results from constrictive bronchiolitis obliterans. The histologic findings are as diverse as the clinical presentation, often complicating diagnosis, which is typically only confirmed by immuno-dermatologic and serologic laboratory findings. Multiple specific effectors of humoral and cellular autoimmunity mediating epithelial damage have been identified. All the evidence to date on the efficacy of therapeutic modalities has rested on individual case reports, small case series, and expert recommendations. An update of advances in clinical and basic research and management of PAMS is provided in this paper; however, it should be noted that PAMS remains a complex and multidimensional disorder requiring further study to distinguish the precise pathogenic mechanisms and the role of neoplasms in them, the mechanisms behind respiratory complications and the accompanying high rate of mortality, as well as to establish unique diagnostic criteria and more effective treatment procedures.

**Key Words:** Paraneoplastic Autoimmune Multiorgan Syndrome, paraneoplastic pemphigus

## Introduction

Paraneoplastic autoimmune multiorgan syndrome (PAMS) is a life-threatening autoimmune blistering disease that in almost all cases is associated with neoplasia. Patients with this rare disorder present severe blistering and painful erosions of the oral cavity, and may display a spectrum of clinical variants of the mucocutaneous disease. This syndrome involves multiple organ systems and its high mortality rate is frequently the result of constrictive bronchiolitis obliterans. Since the histologic findings are as diverse as the clinical presentation, diagnosis is often difficult. The term PAMS includes the signs and symptoms

characterizing this pathogenic procedure and affecting the mucosae, skin and lungs in a heterogeneous group of patients with paraneoplastic disease (1-5). This is the reason why the majority of authors (including those of this review) prefer the term “PAMS” instead of the term “Paraneoplastic pemphigus” which was first described by Anhalt in 1990. Our purpose is to provide an update of advances in clinical and basic research and management of PAMS through a non-systematic literature review. The PUBMED Medline database was searched using keys words including Paraneoplastic Autoimmune Multiorgan Syndrome, paraneoplastic pemphigus and oral manifestations.

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**Citation:** Memis I, et al. Paraneoplastic autoimmune multi-organ syndrome and oral mucosa involvement: an intriguing disorder. *Cancer Research Frontiers*. 2015 Sep; 1(3): 268-279. doi: 10.17980/2015.268

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**Competing Interests:** The authors declare that there are no competing interests.

Received August 30, 2015; Revised November 3, 2015; Accepted November 17, 2015.



**Figure 1.** Painful erosions and ulcerations of the vermilion border of the lips.

The final references were selected according to relevance.

### Epidemiology

PAMS may affect patients of different ages, including children and adolescents (2,6-8), with no specific gender predilection, as supported by a group of authors (8,9). In a study of 42 cases of pemphigus associated with non-thymic neoplasms and another 18 with thymic neoplasms, the mean age of the first group was 56.25 years (range 24-89 years) and the male/female ratio 1.5:1, while in the second group the mean age was 51 years (range 30-86 years) and the male/female ratio was 2.6: 1 (10). Another study (11), reported 18 (10 males, 8 females) cases with a mean age of 59.1 years (range 45-77 years), while a different research group presented 14 cases of children and adolescents between 8 and 18 years with PAMS, with no specific gender predilection, but with an indication that Hispanic children are more susceptible (8). Generally, the age of patients usually ranges between 7-77 years (12) and PAMS in children is mostly associated with Castleman's disease (6-8,13).

### PAMS and Neoplasms

PAMS is directly related to the presence of



**Figure 2.** Non-specific ulceration of the fingers with desquamation of the surrounding skin.

malignancy and in approximately 2/3 of cases the presence of the subsequent neoplasm is recognized prior to the onset of symptoms of PAMS (14-16). Most reported PAMS cases are associated with hematological-related disorders and malignancies (80-84%), including non-Hodgkin lymphoma (3,9-11,13,14,17-23), chronic lymphocytic leukemia (3,9-11,14,17,18,24-26), Castleman's disease (3,7,9,11,14,18,24,25,27-33), thymoma (9-11,17,18,24,34,35), Waldenström's macroglobulinemia (3,9,11,14,18), Hodgkin's lymphoma (10,36) and monoclonal gammopathy (24). The non-hematological neoplasms associated with PAMS (constituting 16% of cases), include carcinomas (adenocarcinomas, squamous cell carcinomas) (11,18,24,25,37-39) and sarcomas (8,11,16-18,35,40,41), like follicular dendritic sarcoma (35,40,41). Additionally, in certain cases more than one underlying neoplasm was involved (18). The range of neoplasms associated with PAMS is presented in Table 1. Interestingly, in disorders like Castleman's disease the presence of PNP is identified as an unfavorable survival risk factor (30). Immunosuppressive therapy, including cyclophosphamide, fludarabine, interferon (2,9,15,16,18) as well as radiotherapy (9,16) can also trigger the onset of PAMS. In addition, various non-neoplastic and/or autoimmune disorders have been associated with PAMS, such as constrictive bronchiolitis, myositis, myasthenia Gravis (9,42,43).

### Clinical characteristics

PAMS is characterized by its great variety of manifestations (2,8,11,13,27). However, oral mucosal lesions are present in almost all patients and are often the first to appear in a series of symptoms (2,9,13,14,16,18). They appear as persistent, painful erosions and ulcerations, affecting the gingivae, the lateral borders of the tongue, and subsequently extend to the entire oral cavity and the vermilion border of the lips, usually in the form of crusts, resembling erythema multiforme or even advanced cases of Stevens-Johnson syndrome (2,11,17,18,23-26,33,39,44,45) (Figure 1). These lesions of the oral mucosa are very painful and resistant to treatment. They can cause dysphagia (2,11,45), significant weight loss (2,45) and are regarded as an important factor in diagnosis (1,2,46). In addition, vesicles, erosions and ulcers are manifested in nasal mucosa and the respiratory system (1,6,9,13,17,46), larynx (1,2,13,45,46), pharynx (1,2,9,11,13,18,46), esophagus (1,2,6,9,11,17,18,46), genitalia (1,2,6,9,17,24,25,33,44), rectum (2,9,33) and conjunctivae (2,9,17,24,26,33).

The cutaneous manifestations are also heterogenous (2,9,17,27,46) and usually follow the

onset of oral mucosal lesions (9,24,46). These manifestations are placed into 5 categories according to the mucocutaneous disease their appearance mimics: i) pemphigus-like, ii) bullous pemphigoid-like, iii) erythema multiforme-like, iv) graft-vs-host disease-like and v) lichen planus-like (1). The blisters usually erupt in waves on the upper trunk, head, neck and proximal extremities (9,13,27,39) (Figure 2). However, non-specific erosions may comprise the

only manifestation at the time of diagnosis (13,46). The blisters on the upper back and chest may coalesce and form larger erosive lesions that, in combination with the always-present oral lesions, may cause difficulty in differential diagnosis from toxic epidermal necrosis (2,13,17). Tense blisters with surrounding erythema can be observed, usually on the extremities, resembling bullous pemphigoid (1,9,12,13,15,46). Lichenoid lesions are mostly

**Table 1. Neoplasms associated with PAMS and related literature.**

Neoplasms	References
<b>Hematologic</b>	
Non-Hodgkin Lymphoma	3, 9-11, 13, 14, 17-23, 46
Hodgkin lymphoma	10, 36
Chronic lymphocytic leukaemia	3, 9-11, 14, 17, 18, 21, 24-26, 46
Castleman's disease	3, 7, 9, 11, 14, 18, 21, 24, 25, 27-33, 46
Thymoma	9-11, 17, 18, 21, 24, 34, 35, 46
Waldenstrom's macroglobulinemia	3, 9, 11, 14, 18, 21
Monoclonal gammopathy	24
<b>Non-hematologic</b>	
<b>Adenocarcinomas</b>	
Pancreas	9
Colon	9, 10
Breast	9, 10
Ovary	10
Prostate	9
Lung	10, 45
<b>Squamous cell carcinomas</b>	
Tongue	9
Skin	10
Cervix	10
Bronchi	2
Urinary bladder	10, 21
Basal cell carcinoma	9
Hepatocellular carcinoma	2
Esophageal	10, 39
<b>Sarcomas</b>	
Liposarcoma	9
Fibrosarcoma	2
Follicular dendritic cell sarcoma	35, 40, 41, 46, 49
Leiomyosarcoma	9
Malignant nerve sheath tumour	2
Malignant fibrous histiocytoma	10
Kaposi's sarcoma	10
Malignant melanoma	9
Inflammatory myofibroblastic tumour	18
Reticulum cell sarcoma	9, 17

found in children (8,9,13), usually located on the trunk and extremities, and include small red scaly papules presenting a lichenoid histologic appearance, mildly pruritic purple papules, widespread papular lesions which may extend to the face and ears, and a generalized reticulate and exfoliative erythema with numerous lichenoid papules on the extensor aspects of the extremities. These lichenoid features are expressed in lesions that have clinical and histological features of erythema multiforme, Stevens-Johnson syndrome and graft-versus-host disease (9,13,46). Additionally, apart from scaly lesions on the palms and soles (2,9,13, 17,18,46) that accompany lichenoid eruptions, there may also be lesions resembling psoriasis (13,46), alopecia (2) and painful paronychia (2,12,13,18). Lesions of varying morphology can coexist in the same patient or transform from one type to another, as the disease progresses (2,9,13,18,46).

#### **Histologic findings (cutaneous and mucosal lesions)**

Histologic features of skin and mucosal lesions exhibit great diversity (13,17,46) and correlate with the major clinical variants of PAMS (i.e. pemphigus-like, pemphigoid-like, erythema multiforme-like, graft-versus-host disease (GVHD)-like and lichen planus-like) (27). The spectrum of the findings ranges from a blistering lesion with only minimal

inflammatory invasion to an even more intense lichenoid monocytic aggregation; typical features of pemphigus vulgaris are also less frequently observed, including acantholysis (6,11,17,21,22,24,27,29, 35,47), intraepithelial blister (6,17,24,27,35) and deposition of autoantibodies in an interepithelial cell pattern (2). Interestingly, dyskeratosis and subepithelial blister can also be found, as in pemphigoid and erythema multiforme (1,21), with accompanying keratinocyte necrosis (6,11,17,21, 24,27,35) and diffuse lymphocytic infiltration of the dermis (1,13,27,35). However, certain cases with lichenoid tissue reaction and minimal or no apparent acantholysis had been referred as PNP (1,5,8,18,21). In those cases, accompanying vacuolization of basal cells (7,11,17,21,28) and perivascular infiltration, mainly of monocytes, in the dermo-epidermal junction, in association with peripheral keratinocyte necrosis without vasculitis (1,5,7,46) present potential diagnostic pitfalls. Melanin containing macrophages may also be present (13,46). Extravasated red blood cells are often seen in papillary dermis (46,47). It has been suggested (24) that the most common histologic finding in PAMS was suprabasilar acantholysis associated with keratinocyte necrosis, interface vacuolar changes or lichenoid infiltrate.

#### **Involvement of respiratory system**

**Table 2. Antigens in the pathogenesis of PAMS in order of reported frequency and cellular location**

Antigens	Molecular Weight (kDa)	Location and Role
Desmoglein	130/160	Transmembrane proteins mediate intercellular homophilic connections (their cytoplasmic part linked to desmoplakins via catenins in the outer dense plaque)
Desmoplakin I	250/210	Mediate connection between desmosomes and intermediated filaments of cytoskeleton (inner desmosomal plaque)
Envoplakin	210	Members of plakin family (inner dense plaque)
Periplakin	190	
*BPAG1	230	Hemidesmosomal plaque: Ligands for transmembrane hemidesmosomal proteins
Plectin	>400	

\*Bullous pemphigoid antigen 1

**Table 3: Most common vesiculoulcerative diseases with oral involvement in the differential diagnosis of PAMS**

Disease	Clinical characteristics	Histologic features	Main targets for autoantibodies	Immuno-fluorescence (*DIF, **IIF)
<b>PNP</b>	Vesicles, erosions /ulcerations affected any mucosa and/or skin. Not sudden onset	Subepithelial and intraepithelial vesicles	Dsg3, Dsg1 Envoplakin Periplakin BPAG1, Plectin Desmoplakins I/II	DIF: Positive intercellular and basement membrane zone IIF: Positive
<b>Pemphigus vulgaris</b>	Vesicles and erosions/ulcerations affected any mucosa and/or skin. Not sudden onset	Intraepithelial vesicles, Tzanck cells	Dsg-3 (mucosal involvement) Dsg3+Dsg1 (mucosal + cutaneous involvement)	DIF: Positive intercellular IIF: Positive
<b>Erythema multiforme</b>	Vesiculoulcerative lesions affected any mucosa or skin (target lesions). Sudden onset.	Non-specific, intra- and subepithelial vesicles, subepithelial oedema, perivascular infiltration	Non-specific	DIF: Non specific IIF: Negative
<b>Mucous membrane pemphigoid</b>	Mucosal Vesiculoulcerative lesions affected any mucosa (mainly oral, conjunctival mucosas). Not sudden onset.	Subepithelial vesicles with mild chronic inflammation	BP230, BP180, $\alpha$ 6-integrin, laminin 5, 6, 168kDa 205kDa, b4-integrin	DIF: Positive, basement membrane IIF: Negative
<b>Bullous pemphigoid</b>	Cutaneous Vesiculoulcerative lesions rarely affecting oral or other mucosas. Not sudden onset.	Subepithelial vesicles, acute and chronic inflammation and presence of eosinophils within vesicles	BP230, BP180	DIF: Positive, basement membrane IIF: Positive
<b>Lichen Planus</b>	Lesions range from whitish papules and striae to erosions, ulcerations and plaques or atrophy. Not sudden onset.	Hyperkeratosis, rete ridges like saw-toothed, epithelial vacuolation and apoptosis, subepithelial band-like lymphocytic infiltration	None /unknown	DIF: basement membrane (fibrinogen) IIF: Negative

\*DIF: Direct Immunofluorescence, \*\*IIF: Indirect Immunofluorescence

Respiratory involvement occurs in about 20-40% of PAMS patients, especially with the clinical features of bronchiolitis obliterans (1,7,12,19,48). It is a late complication which persists even after the tumour has been excised/treated and in spite of the immunosuppressant therapy (19). In most cases, the outcome is respiratory failure and death (7,23,32,44,48). Possible causes of respiratory failure include infection, toxic effects induced by chemotherapy, neoplasia and autoantibody mediated pulmonary injury (7,19,37,47,48).

The exact mechanism of respiratory involvement is not clear yet. Keratin 14-positive basal epithelial cells of bronchi undergo dyskeratotic changes, detach from the lamina propria and their neighboring cells and are aspirated distally where they obstruct the lumen of the intermediate and small airways and occlude alveolar sacs (1). Some scientists have suggested that autoantibodies against plakin proteins are involved (1,14,19), while important role is played by the basal layer inflammatory infiltration of respiratory epithelium (1). Other unknown

transmembrane proteins of respiratory epithelium (12) or mechanisms of cell-mediated immunity that expose intracellular plakin proteins to the immune system may also be involved (7).

Recently, Hata et al showed that squamous metaplasia after pulmonary epithelial injury may extend the autoimmune reaction from skin and mucosa to lungs due to ectopic expression of epidermal antigens, in a mouse model (49).

Histopathological features include acantholysis of bronchial epithelium (1,6,7,19) and sometimes deposition of IgG (6,7,19) and complement in the respiratory epithelia forming a linear manner on the respiratory-epithelial-cell surfaces as well as a linear and granular manner along the lamina propria. Inflammatory infiltration of lymphocytes, neutrophils, eosinophils, plasma cells and histiocytes, as well as fibrosis around bronchioles are also characteristic findings (1,19,46).

The earliest symptoms are progressive dyspnea, initially associated with an absence of findings on chest radiography (19). Other common symptoms are dry cough and decreased blood PO<sub>2</sub> (32,46). Not unusually, despite the immunosuppressive therapy the lesions progress to tracheal and bronchial inflammation leading to gradual deterioration of pulmonary function, hypoxia and, finally death (19).

### Pathogenesis

The exact pathogenetic mechanisms of PAMS are still unknown, while a variety of pathophysiological mechanisms have been proposed. A lymphoproliferative neoplasm can either dysregulate the immune system with the involvement of several cytokines (mainly IL-6) leading to the production of autoantibodies that damages the cell membranes (14,37,50), or produce antibodies targeting desmosomal and hemidesmosomal proteins of the normal epithelial cells (29,46,47). A research study (29) showed that specific clones of B-cell in Castleman tumors produced in-vitro autoantibodies against proteins of desmosomes and hemidesmosomes with the same or similar specificity as that of autoantibodies in the patients' sera. Interestingly, the existence of expanded rough-surfaced endoplasmic reticulum in plasma cells and B cells in tumors such as thymoma and follicular dendritic cell sarcoma has supported their ability for antibody secretion and, according to the authors, this finding is considered as a cornerstone in the pathogenesis of PAMS (35). These observations were further supported by another group (46), who found that the B-cell tumors have a similar recombinant variable region of immunoglobulin gene.

However, a more general proposed pathogenic

mechanism indicates the production of antibodies from the immune system against strong immunogenic epitope created by somatic mutation in cancer cells in patients with moderated MHC type as shown in cases of cancer and scleroderma (51) and, similarly, it can be hypothesized that epithelial proteins expressed by tumor cells and cross-reaction with antigens of normal epithelial cells may occur in PAMS (2,6). In this case, an epithelial tumor would be expected to have antigens that are recognized in PAMS: desmoplakins, periplakin, envoplakin, desmogleins and plectin. These antigens could be targets for antibodies produced against the tumor, which will be directed also against the corresponding antigens of the epithelium (50). However, it must be pointed out that the majority of PAMS-associated neoplasms are lymphoid malignancies (2,18). Furthermore, in most cases of malignancy, the host immune response is attenuated by the tumor, so that autoimmunity and development of PAMS is not expected to occur (2).

Another mechanism, which is often found in the literature associated with the pathogenesis of PAMS is the epitope spreading (1,2,25,52). It is a phenomenon in which an initial autoimmune or inflammatory process can cause tissue damage, resulting in exposure of specific protein components - normally 'hidden' from the immune system - and a secondary immune response initiation (52). In this case, an obvious synergy exists between humoral and cellular immunity (1,2,4,25). It has been found that antibodies against the transmembrane proteins desmoglein 1 (Dsg1) and 3 (Dsg3), after connecting to the cell membrane of keratinocytes and destroying it, allow the exposure of the plakin family of proteins and production of autoantibodies against them (13). The primary stimulus may also be either an attack from cytotoxic T-cells, which cause damage to basal layer epithelial cells and expose autoantigens to the immune system, triggering the production of autoantibodies, or autoantibodies, which trigger antibody-dependent cell-mediated immunity (antibody-dependent cellular cytotoxicity, ADCC), something that leads to cellular damage and promotes the proliferation of epitopes (5). This hypothesis is supported by the inflammatory nature of the lesions in PAMS, in contrast with the pemphigus vulgaris (PV), where lesions usually develop in normal skin (13). For the interpretation of the mechanism of epitope spreading several mucocutaneous inflammatory diseases such as lichen planus have been implicated (25,38). It has been proposed two possible explanations: 1) A pre-existing and chronic lichenoid reaction in the skin can predispose some patients with cancer to develop humoral

autoimmunity to components of the basement membrane and/or 2) an underlying neoplasm may trigger the development of a cell mediated lichenoid dermatitis, exposing autoantigens and making them susceptible to recognition by the autoreactive T-cells, leading to activation of B cells and antibody production (25).

The cells that appear to be involved in the previous mechanism are CD8 + cytotoxic T-lymphocytes, CD68+ macrophages and CD56+ natural killer cells (1,2,4,9). These are similar to those found in lichenoid infiltrates of erythema multiforme, lichen planus and graft-versus-host disease (1). The local production of inflammatory mediators interferon-gamma and TNF- $\alpha$  (5) has also been observed. The activation of these cells is induced by the interleukin-6, which is strongly increased in serum of patients with PAMS (14,53). This cytokine, among others, promotes the differentiation of B and T cells and production of immunoglobulins, something that suggests involvement in the dysregulation of the immune system (50,53).

Inducible nitric oxide synthase (iNOS) holds an important role in the pathophysiology of this mechanism. Nitric oxide sensitizes the target cells in apoptosis and is the main mechanism by which target cells are killed by activated cytotoxic cells. In lesions of PAMS, iNOS-positive cells are found throughout the epidermis and thus could be targeted by cytotoxic cells that infiltrate the skin. The iNOS-positive keratinocytes were localized in the basal layer, which is the exact location of the loss of epidermal adhesion in patients with PAMS (1).

### Immunological features

Immunological features of PAMS arise from the findings of direct immunofluorescence (DIF), indirect immunofluorescence (IIF) and immunoprecipitation (immunoblot) analysis. Three main patterns on DIF have been reported. These are: 1. IgG autoantibodies, with or without complement, on the keratinocyte cell surface of lesional skin, 2. IgG and/or complement along the basement membrane zone. 3. A combination of the above two patterns (6,12,13,24).

On IIF serum, autoantibodies of patients with PAMS react with proteins of stratified squamous epithelia, transitional, columnar and simple epithelia (1,2,12,17). Commonly used substrates include the stratified squamous epithelium of monkey esophagus or human skin, mouse tongue and the transitional epithelium of rat bladder (2,12,17,22,24). The prevalence of positive IIF staining varies with the substrate used. IIF staining of rat bladder found to be highly sensitive (75- 86%) and specific (83-100%)

for a diagnosis of PAMS and serves as a useful diagnostic tool (2,24).

The originally described immunoprecipitation bands corresponded to antigens with molecular weight of 250kDa (Desmoplakin I), 230kDa (Bullous pemphigoid antigen I or BPAg1), 210kDa (Desmoplakin II and Envoplakin) and 190kDa (Periplakin) (17). As more cases have been reported and investigated, new polypeptides have been added. These are polypeptides with molecular weight of >400kDa (Plectin), 170kDa (recently identified as the protease inhibitor alpha-2-macroglobuline-like 1, A2ML1), 130kDa (Desmoglein 3 or Dsg3), 160kDa (Desmoglein 1 or Dsg1) (1,7,12,21,24,35,37,47,50, 55). In Table 2 the known antigens implicated in the pathogenesis of PAMS are presented in order of reported frequency and cellular location (13). Not all the polypeptides mentioned above are required for disease expression, but they, usually, occur in various combinations (2,5,25). The variety of antigens involved and their combinations may be the reason of the diversification of mucocutaneous lesions (1). Antibodies to Dsg-3 (anti-Dsg3) occur in the majority of cases and antibodies to Dsg 1(anti-Dsg1) are found in approximately two-thirds of cases (13). Enzyme-linked immunosorbent assay (ELISA) is more sensitive and specific than convention immunoprecipitation for the detection of antibodies against Dsg1 and Dsg3 (24,54). It has been supported that immunoblotting detection of autoantibodies against envoplakin and periplakin is highly sensitive (82%) and specific (100%) diagnostic feature (24).

Whereas antibodies against Dsg1 and Dsg3 are key molecules in the pathogenesis of pemphigus vulgaris, some investigators believe that these antibodies play a significant primary role in the pathogenesis of PAMS, too (12,13,15,24,50). Amagai et al showed that anti-Dsg3-specific antibodies that were affinity purified from PNP patients' sera were pathogenic and caused blisters and erosions when injected in neonatal mice showing suprabasilar acantholysis in histology. Human IgG deposition was found not only on keratinocyte cell surfaces and basement membrane zone but also in the cytoplasm. Interestingly, the incubation of sera anti-Dsg-3 and anti-Dsg-1 antibodies with a mixture of recombinant Dsg3 and Dsg1 epitopes before injection into neonatal mice was sufficient to eliminate the ability of PNP sera to induce cutaneous blisters in neonatal mice in vivo (54). This suggests that autoantibodies against Dsg-3 and Dsg-1 have a key role in pathogenesis of PAMS. These antibodies are responsible for the initial disruption of keratinocyte membrane and the exposure of the intracellular proteins of plakin family, which induce

a secondary autoimmune response (12,54). There are several controversial reports concerning the detection of both Dsg 3 and Dsg 1, and their significance, in the patients' serum, in several cases of PAMS (5,21,22). There is mounting evidence that antibodies detected in PAMS do not necessarily mediate the pathological process directly, but may serve as serological markers of disease (1,2,7,29). These findings indicate that the loss of epithelial adhesion and the development of inflammatory lesion in the epithelial tissues of patients with PAMS require participation of both humoral and cellular autoimmunity effectors.

### Diagnosis

Over the years, a plurality of diagnostic criteria have been proposed (5,8,17,46,56), leading to the conclusion that there is no overall consensus on diagnosis. However, the most commonly accepted criteria were proposed by Anhalt (17) and later revised by Camisa and Helm (56). They divided the diagnostic criteria of PAMS into 3 major and 3 minor signs (56). Among them, three major or two major and two minor signs are required for the diagnosis including the polymorphic mucocutaneous lesions, the concurrent neoplasm and serum antibodies with a specific pattern of immunoprecipitation as major signs and histologic evidence of acantholysis, direct immunofluorescence (DIF) showing intercellular and basement membrane staining, and indirect immunofluorescence (IIF) with rat bladder epithelium as minor criteria, respectively. Also, several additional findings have been proposed (8), including the identification of autoantigens envoplakin (210kDa), periplakin (190kDa), plectin (466kDa), desmoglein-3 (130kDa) and desmoglein-1 (160kDa), lichenoid variant of the disease and signs and symptoms of respiratory involvement as well. Due to the extensive variability of signs in PAMS, the following criteria have been proposed as the minimal ones for diagnosis of the syndrome:

1. Painful, progressively increased oral manifestations, with preferential involvement of the tongue.
2. Histologic features of acantholysis or lichenoid or interface dermatitis.
3. Demonstration of plakin autoantibodies.
4. Co-existent lymphoproliferative neoplasm (14).

Even though there have been significant advances in detailing the immunopathology of the disease, certain key features of the seminal description remain constant (2,8). These include:

1. Mucocutaneous manifestations (especially intractable stomatitis).
2. Identification of a concurrent neoplasm

(especially lymphoproliferative).

3. Laboratory evidence by immunoprecipitation of proteins corresponding to components of epithelial cell junctions (hemidesmosomes and desmosomes).
4. Progressive disease that is refractory to treatment with a fatal outcome in most cases.

The variety of clinical and histopathologic features of PAMS is responsible for problems of differential diagnosis between PAMS and other mucocutaneous diseases. The differential diagnosis includes pemphigus (vulgaris or foliaceus) (14,46), erythema multiforme/Steven-Johnson syndrome (11,14,46) and toxic epidermal necrolysis (11,14), bullous pemphigoid (11), lichen planus (bullous and erosive forms)(11,14,46), aphthous stomatitis (14), epidermolysis bullosa aquisita (11), dermatitis herpetiformis (11), linear IgA bullous dermatosis (11), cicatricial pemphigoid (11), graft vs host disease (46), and bullous drug eruption (11,14). The most important characteristics of common vesiculoulcerative diseases affecting oral mucosa that may implicate in differential diagnosis of PAMS are summarized in Table 3.

### Prognosis

Prognosis of patients with PAMS is generally poor (3,6,7,8,19,25,57) and may depend on the related neoplasm (neoplastic grading), the severity of the disease and on the presence of respiratory complications (9,14,57). Cases of PAMS associated with benign tumours, like thymoma or Castleman's tumour, improve or remit when the tumour is managed (25,47). On the other hand, in malignancies, the mortality rate is around 90% up to 2 years after initial diagnosis (19), since treatment of the underlying malignancy is often not linked to an improvement of the disease (27). The cause of death is associated with complications of immunosuppressive therapy, like sepsis, gastrointestinal bleeding, multi-organ failure and respiratory failure (14,19).

### Treatment

Therapy of PAMS is directed towards both underlying neoplasm and Paraneoplastic mucocutaneous manifestations, considering that treatment of the underlying neoplasm results to PAMS resolution (2).

The subtype of neoplasm is critical and in cases of neoplasms with benign behavior, like thymoma and Castleman's tumour, the early surgical excision of the tumour alone may lead to remarkable improvement of the symptoms (1,18,29,46,47). The intravenous administration of immunoglobulin (IVIG) before,



during and after the surgical procedure is recommended (14,29,46,47). On the other hand, particularly in cases of malignant neoplasms, high doses of corticosteroids have been considered as effective (10,12,14,20). Other interventions include the use of immunosuppressive agents such as cyclophosphamide, cyclosporine, azathioprine, gold, dapsone, methotrexate (11), triamcinolone acetonide (10), thalidomide and chlorambucil (6). Furthermore, immunoapheresis, plasmapheresis or photopheresis have been used with limited results (11,15,18). Mycophenolate mofetil may improve the symptoms of PAMS alone or in combination of other immunodepressants (1,6,20). Fludarabine has been used with ambiguous results, as there has been reported that it caused a flare up of the symptoms (14,20).

Rituximab, an anti-CD20 agent is gaining ground as a therapeutic option of PAMS when B-cell lymphoma is involved (7,15,18,20,40). Although the exact mechanism of action of rituximab is unclear, it is believed that the improvement observed in PAMS patients may be due to either the reduction of neoplastic B cells or to a decrease in the abnormal immune response related to the reduction of normal CD20-positive B cells. It is administered intravenously in a dose of 375mg/m<sup>2</sup>/week for 4 weeks. Nausea, hypotension, rash, fever, chills, headache, bronchospasm and hypotension have been reported as adverse reaction (20). It is often administered in combination with corticosteroids or other therapeutic patterns (7,40).

Newer biologic agents include Alemtuzumab, a recombinant DNA-derived humanized monoclonal antibody that is directed against the cell surface glycoprotein CD52 of normal and malignant B and T cells and Daclizumab, an IL-2 receptor antagonist which targets activated T cells. Furthermore, cholinomimetic agents, like pyridostigmine, may be another useful treatment option for PAMS (2,5,27).

Generally, it is important to emphasize that cutaneous lesions improve before lesions of oral mucosa, which are refractory, and bronchiolitis obliterans (2,12,14). In order to manage respiratory insufficiency, lung transplantation has been used with encouraging results in a 14-year-old boy with PAMS and Castleman's disease (3).

### Conclusion

Paraneoplastic autoimmune multiorgan syndrome (PAMS) is a disorder, which demands the cooperation of various specialists, like dentist, oral pathologist, dermatologist, ophthalmologist and

oncologist. Intraoral lesions are found in almost all PAMS cases and in 45% of cases they are the first sign (24), often mimicking the clinical feature of erythema multiforme / Stevens Johnson's syndrome, lichen planus, bullous pemphigoid or pemphigus vulgaris. The presence of painful and persistent oral lesions that do not meet the necessary criteria to be classified in a particular disease should arouse suspicion in the physician for a possible diagnosis of PAMS, even though at that time an underlying neoplasm has not been found, since it happens in about 1 / 3 of cases and pemphigus may precede the clinical manifestations of the underlying neoplasm by several months (11). Besides, it is not an absolute requisite that a full spectrum of manifestations of the syndrome appears from the beginning.

The evaluation for the diagnosis of the syndrome should include detailed history, physical examination, complete blood count, electrophoresis of serum proteins and computed tomography of the chest, upper and lower abdomen and pelvis, skin biopsy for routine histologic examination, direct immunofluorescence, indirect immunofluorescence and/or more specific methods, including immunoprecipitation/immunoblotting. However, it should be noted that PAMS remains a complex and multidimensional disorder, and further study is necessary in order to distinguish the precise pathogenic mechanisms and the association of neoplasms with them, the mechanisms behind respiratory complications and the high rate of mortality that accompany them, the establishment of unique diagnostic criteria, as well as more effective treatment procedures.

### Acknowledgements

We would like to thank Dr Loumou Panagiota, MD, DDS, PhD(Oral Med), 2<sup>nd</sup> Dermatology Clinic NKUA "Attiko" Hospital of Athens, Greece for the clinical figures.

### Abbreviations list:

PAMS	Paraneoplastic autoimmune multiorgan syndrome;
PNP	Paraneoplastic Pemphigus;
IL	Interleukin;
PV	Pemphigus Vulgaris;
GVHD	graft-versus-host disease;
dsg1	desmoglein 1;
dsg3	desmoglein 3;
DIF	direct immunofluorescence;
IIF	indirect immunofluorescence;
BPAG1	Bullous Pemphigoid Antigen 1.

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