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REVIEW ARTICLE

Paraneoplastic Pemphigus

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Abstract

Paraneoplastic Pemphigus (PNP) is an autoimmune-related acquired bullous disease associated with neoplasia. Both humoral and cellular immunity are involved in the pathogenesis of PNP. Characteristically, PNP has a diverse spectrum of clinical and immunopathological features. Suprabasal acantholysis and clefts with scattered necrotic keratinocytes are the unique histopathological features. PNP patient sera recognize multiple antigens, which have been identified as the plakin protein family. Non-Hodgkin's lymphoma, Castleman's disease, thymoma, follicular dendritic cell sarcoma and chronic lymphocytic leukemia are the commonly associated neoplasms in PNP. The treatment of PNP to date has been rather disappointing. For patients with Castleman's disease, the early detection and removal of the tumor are critical for the treatment of PNP.

Keywords

Paraneoplastic pemphigus, Stomatitis, Direct immunofluorescence, Indirect immunofluorescence, Rat urinary bladder, Plakin protein, Non-Hodgkin's lymphoma, Castleman's tumor, Thymoma, Follicular dendritic cell sarcoma, Chronic lymphocytic leukemia, Corticosteroids, Resection

Introduction

Paraneoplastic Pemphigus (PNP) is a debilitating and lethal adult and pediatric autoimmune blistering skin disease that occurs in the setting of a known or occult neoplasm especially lymphoproliferative neoplasms [1]. In 1990, Anhalt, et al. [2] described five atypical pemphigus cases which were associated with lymphoproliferative disease. Anhalt called this disease paraneoplastic pemphigus. The term Paraneoplastic Autoimmune Multiorgan Syndrome (PAMS) was suggested later by Nguyen, et al., given that is not a skin disease, but a syndrome characterized by the presence of mucocutaneous and non-cutaneous pathology associated with neoplasia [3]. More than 260 case reports of PNP have been documented since that time [1,4,5] and about 20 of the reported patients were children or adolescents. Yet PNP may be more common than is generally believed given that serum detection of autoantibodies is only performed by a handful of laboratories. One clinical sign is severe stomatitis, although other skin changes can vary considerably. Suprabasal acantholysis and clefts with scattered necrotic keratinocytes are the unique histopathological features. Autoantibody activity in PNP is complex, but usually highly characteristic [2,6-8]. PNP patient sera recognize multiple antigens, which have been identified as the plakin protein family that includes desmoplakin, bullous pemphigoid antigen I, envoplakin and periplakin, and desmogleins 1 and 3. Non-Hodgkin's lymphoma, Castleman's tumor, thymoma, follicular dendritic cell sarcoma and chronic lymphocytic leukemia are the commonly associated neoplasms in PNP [2]. These clinical characteristics, in addition to positive immunophenotypic findings make the diagnosis of PNP. The treatment of PNP to date has been rather disappointing. The mortality rate associated with the disease is high and common causes of death include sepsis, gastrointestinal bleeding, and bronchiolitis obliterans [6,9]. The aim of this article was to evaluate the clinical, pathological and immunological characteristics of PNP based on the analysis of literature reports.

Mucosal Involvement

The clinical presentation of PNP, although highly

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Figure 1: Severe erosion, ulcer and crusts on lips.

Figure 2: Severe erosion, ulcer on prepuce.

varied, typically begins with a florid, painful eruption of mucous membrane lesions, which may involve the oropharynx, nasopharynx, tongue, vermillion of the lips (Figure 1), conjunctiva, anogenital region (Figure 2), or esophagus [1,4,10,11]. Oral mucosal lesions were usually more extensive than that of pemphigus vulgaris or erythema multiforme. In addition to conjunctivitis, ocular presentation also included corneal ulceration, which was successfully managed with topical tacrolimus, cyclosporine and systemic methylprednisone, thalidomide, methotrexate in a case reported [12]. Severe stomatitis can be one of the hallmarks of PNP.

Cutaneous Lesions

The onset of cutaneous lesions has a variable delay after the appearance of mucous membrane lesions, ranging from days to months [1,2,4]. Cutaneous features of PNP are polymorphic, including vesicles, blisters, erosions, patches, papules and plaques. The Nikolsky sign may be absent. The heterogeneity in the presentation of the cutaneous manifestations of this disease has led to a stratification of PNP based on variable and polymorphic features that mimicked Pemphigus Vulgaris (PV), Pemphigus Foliaceus (PF), Bullous Pem-

phigoid (BP), Erythema Multiforme (EM), lichen planus and Graft-versus-Host Disease-like [11]. Specifically, (i) Pemphigus-like: superficial vesicles, flaccid blisters, erosions and crusts, occasional and limited erythema; (ii) Bullous pemphigoid like: scaling erythematous papules that may be associated or not with tense blisters; (iii) Erythema multiforme-like: polymorphic lesions, mainly scaling erythematous papules with erosions or occasionally ulcers with difficult healing; (iv) Lichen planus-like: small squamous flat-topped violaceus papules and intense involvement of mucosal membranes; (v) Graft-versus-Host Disease-like: disseminated dusky red scaly papules [3]. These cutaneous manifestations often present in waves of lesions and, in contrast to pemphigus vulgaris, blisters in PNP do not arise from normal skin but typically develop from inflammatory papules or macules, which greatly outnumber bullous eruptions in PNP on individual patients [13]. Cutaneous syndromes are characterized by blister formation due to an autoimmune response to components of the epidermis or basement membrane in the context of a neoplasm.

Systemic Involvement

There has also been well-documented evidence of involvement of internal organs, such as lungs, smooth muscle, thyroid, kidney, and gastrointestinal tract [11]. Bronchiolitis Obliterans (BO) is the most common complication and progressive respiratory failure caused by BO is the most important cause of death. Evidence to date indicates that in paraneoplastic pemphigus, autoantibodies directed against plakin proteins may be responsible for acantholytic changes in the respiratory epithelium, among which, epiplakin and desmoglein3 might be the major autoantigens [14-16]. Moreover, there is an increased occurrence of Castleman's disease in patients with pulmonary complications [17]. Myasthenia Gravis (MG) is a complication of PNP related to its neurological involvement. A recent research [18] about MG and its correlation in patients with PNP revealed that overall 39% of patients with PNP experienced muscle weakness, 35% were diagnosed with MG, and MG complications did not affect the overall survival percentage in PNP. Another term for PNP, Paraneoplastic Autoimmune Multiorgan Syndrome (PAMS) has been proposed by Nguyen, et al., given that it is not a skin disease, but a syndrome characterized by the presence of mucocutaneous and non-cutaneous pathology associated with neoplasia [3]; and in PNP the autoantibodies bind in the kidney, as well as to the epithelium of colon, the small intestine, thyroid, striated muscle and smooth muscle [11].

Histopathology

The histologic findings from patients with different clinical presentations of PNP have shown similarities with other known dermatologic conditions (Figure 3), perhaps indicating commonalities in pathogenesis.
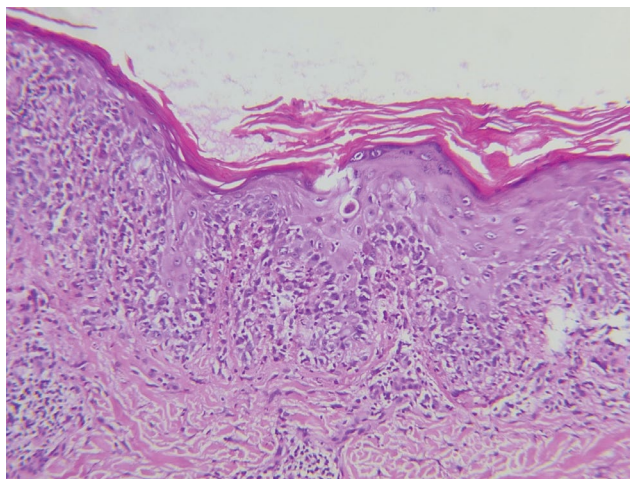
Figure 3: Necrotic keratinocytes and acantholysis.

Figure 4: Indirect immunofluorescence using rat bladder epithelium as substance showing intercellular immunoglobulin G deposition.

There may be intraepidermal cleft and acantholysis, or more rarely, subepidermal blisters. The clinical variants also have their respective histological features: (i) Pemphigus-Like: intra-epidermal cleft surrounded by mononuclear cells; ii) Bullous pemphigoid-like: subepidermal cleft with or without basal cellular vacuolization, and moderate mononuclear infiltrate in dermo-epidermal junctions; (iii) Erythema multiforme-like: dyskeratosis without cleft or with areas of epidermal separation, due to basal cell disintegration, and distinct perivascular infiltrate; (iv) Graft versus host disease-like: absence of epidermal separation, hyperkeratosis or hyperparakeratosis and dyskeratosis with or without vacuolar degeneration of basal cell layers and intense mononuclear interface dermatitis; (v) Lichen planus-like: hypergranulosis, dyskeratosis and lichenoid mononuclear infiltrate [3,19].

It is now accepted both autoantibody-mediated humoral immunity and cell-mediated immune mechanisms play a role in the development of PNP. The underlying immunological mechanism may shed light on the spectrum of clinical and histological features for a given case of PNP [20,21]. According to the dominant mechanism of cytotoxicity, pemphigus-like or LP-like features may be prominent. If the cytotoxicity is mediated by autoantibodies, a pemphigus-like clinicopathological presentation is prominent. In contrast, if the dominant mechanism is cell-mediated cytotoxicity, LP-like lesions may be prominent [22].

Direct Immunofluorescence

Direct Immunofluorescence (DIF) of a perilesional biopsy shows a typical pemphigus pattern with intercellular deposits of IgG/C3 in the epithelium and deposits of IgG/C3 with the same pattern in sweat gland ducts have recently been reported [23]. In addition, there may be linear deposits of IgG and/or C3 in the basement membrane zone, may reflect of the reactivity with BP230 [2]. Both patterns were seen in our patients. In patients 1 and 3, the results of DIF are negative and thus it is not a necessary diagnostic criterion for PNP [6-8].
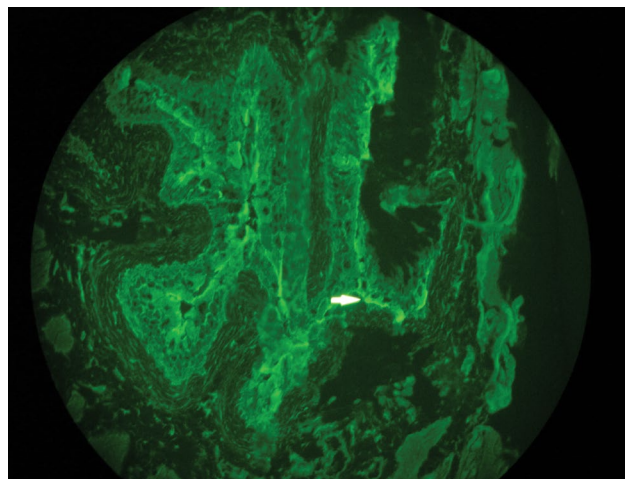
Indirect Immunofluorescence

In all forms of pemphigus Indirect Immunofluorescence (IIF) on monkey esophagus shows characteristic intercellular binding of IgG and often C3 in the epithelium. Given the strong expression of plakins, rat or monkey urothelium is the most appropriate substrate for screening for antibodies to PNP (Figure 4) [8,24]. Sera from patients with pemphigus vulgaris or foliaceus do not react with urothelium. If a specific detection system for autoantibodies to envoplakin or periplakin is not available, detection of anti-plakin-antibodies on IIF on rat or monkey bladder is necessary for diagnosis of PNP.

Multiple Antigenic Targets

Autoantibodies to plakins are characteristic and diagnostic of PNP [2]. As structural components of desmosomal and hemidesmosomal plaques, their interaction with the keratin cytoskeleton of keratinocytes can result in the suprabasal clefting seen in PNP if affected by autoantibodies. The specific autoantibodies to plakins correlated with PNP include: desmoplakin I (250 kd), bullous pemphigoid antigen I (230 kd), desmoplakin II (210 kd), envoplakin (210 kd), periplakin (190 kd), plectin (500 kd), desmogleins (Dsgs) 1 and 3, and a 170-kd protein. This 170-kd protein has recently been identified as alpha-2-macroglobulin-like-1 (A2ML1), a broad range protease inhibitor expressed in stratified epithelia and other tissue damaged in PNP [25,26]. In 2016 a Japanese study indicated that epiplakin is one of the major PNP autoantigens and is related to PNP-related bronchiolitis obliterans [16]. A large cohort of 104 patients with PNP found statistically significant correlations between positive desmoglein 3 reactivity and genital lesions, and between positive desmoglein 3 reactivity and bronchiolitis obliterans [14].

Of those, the most specific for PNP is autoantibodies to envoplakin [27] and periplakin [28], followed by desmoplakin 1 and 2 [29], plectin [30], and a 170-kD pro-

tein [2]. Based on Joly and colleagues' study of 22 PNP patients [8], the presence of autoantibodies to periplakin or envoplakin was 82% sensitivity and 100% specificity. However, in a case reported by Sanz-Bueno J, et al., a patient with paraneoplastic autoimmune multiorgan syndrome secondary to a lymphoblastic T- cell lymphoma, had no detectable autoantibodies, who presented with a lichenoid dermatitis and vitiligo, later developing bronchiolitis obliterans and autoimmune hepatitis [31].

Associated Tumors

PNP is an autoimmune syndrome mostly seen in association with hematologic neoplasms including Castleman's disease [5,8,29,32-48], Non-Hodgkin's lymphoma [1,2,8,29,34,36,49-63], chronic lymphocytic leukemia [2,8,29,34,36,51,64-71], thymoma [1,2,5,8,29,34,46,66,72-77], Waldenstrom's macroglobulinemia [78-81], monoclonal gammopathy [8], Hodgkin's lymphoma [82], and centroblastic lymphoma [1]. Castleman's disease associated with paraneoplastic pemphigus is misdiagnosed frequently and easily in clinical practices. Furthermore, the mortality rate for this disease is very high. In a pediatric age group, paraneoplastic pemphigus has a striking association with Castleman disease and has a particularly poor prognosis in this age group [83].

The Nonhematologic neoplasms associated with PNP include follicular dendritic cell sarcoma [5,42,46,47,72,84,85], inflammatory myofibroblastic tumor [86], leiomyosarcoma [87], liposarcoma [88], malignant nerve sheath tumor [89], inflammatory fibrosarcoma [90], reticulum cell sarcoma [91], and malignant melanoma [92], squamous cell carcinoma of the vagina [93], and adenocarcinoma of the colon [55], prostate [94,95], pancreas [88,93], breast [36], and lung [96,97] (Table 1). Follicular Dendritic Cell Sarcoma (FDCS) is a rare tumor associated with paraneoplastic pemphigus. It is an uncommon neoplastic proliferation of spindled to ovoid cells with morphologic and immunophenotypic features

similar to normal follicular dendritic cells. While most follicular dendritic cell sarcomas arise from lymph nodes, at least one-third occur in extranodal sites. Inflammatory Myofibroblastic Tumour (IMT) is a rare low-grade sarcoma of fibroblasts and myofibroblasts associated with inflammatory cells, most commonly occurring in the lung. In a study [98], a case of PNP associated with IMT of the mediastinum was reported and the patient had a favourable outcome following surgical resection and treatment with a systemic steroid, azathioprine, and i.v. immunoglobulin.

Diagnostic Criteria

In 1990, Anhalt initially proposed five criteria for the definition of a PNP case [2]: (1) Painful mucosal erosions and polymorphous skin eruption in the context of a neoplasia; (2) Histological changes (acantholysis, keratinocyte necrosis, interface dermatitis); (3) DIF showing IgG and complement deposition in intercellular substance and basement membrane zone; (4) IIF with the same deposition as for DIF, in skin, mucosa and simple, columnar, and transitional epithelium and (5) Demonstration of serum antibodies through immunoprecipitation of a complex of four keratinocyte proteins (250, 230, 210 e 190 kd). In 2004, Anhalt proposed minimal diagnostic criteria for PNP [29]. (1) Clinical: painful progressive stomatitis with preferential involvement of tongue; (2) Histological: acantholysis or interface dermatitis; (3) Immunological: presence of antiplakin antibodies (at least periplakin and envoplakin). The pivotal criterium of PNP is autoantibodies directed against desmosomal plakin proteins: desmoplakin I (250 kDa), desmoplakin II (210 kDa), envoplakin (210 kDa), periplakin (190 kDa), and α2macroglobulin-like-1 protein (170 kDa). In addition, autoantibodies against Dsg-1, Dsg-3, plectin and 230 kDa bullous pemphigoid antigen can be detected. These antiplakin antibodies should be revealed by immunoprecipitation or immunoblotting, in addition to positive IIF in monkey esophagus and rat bladder. Anti-Dsg-3 ELISA may also be positive, but this does not discriminate between PNP and other pemphigus variants (PV and PF). (4) Association with lymphoproliferative disorder: Non-Hodgkin's lymphoma and chronic lymphocytic leukemia generally in cases with previous diagnosis (2/3 of cases), and Castleman's disease, abdominal lymphoma, thymomas or retroperitoneal sarcoma in cases with occult neoplasia at the time of diagnosis of PNP (1/3 of cases) [3].

Treatment Options

Patients with a diagnosis of PNP without previous diagnosis of a neoplasia - about 17% of PNP cases - must be investigated with complete blood count with differential leukocyte, serum protein electrophoresis, computerized tomography (chest, abdomen, and pelvis), and biopsies of bone marrow, lymph nodes, or solid tumor, according to indication [3].

Table 1: Paraneoplastic pemphigus: associated neoplasms.

A	Hematologic neoplasms
	Castleman's disease
	Non-Hodgkin's lymphoma
	Chronic lymphocytic leukemia
	Thymoma
	Waldenstrom's macroglobulinemia
	Monoclonal gammopathy
	Hodgkin's lymphoma
B	Nonhematologic neoplasms
	Adenocarcinoma of the colon
	Adenocarcinoma of the prostate
	Adenocarcinoma of the pancreas
	Adenocarcinoma of the breast
	Squamous cell carcinoma of the tongue
	Squamous cell carcinoma of the vagina
	Basal cell carcinoma of the skin
	Bronchogenic carcinoma
	Malignant melanoma

The prognosis of PNP is generally poor, and the disease is often fatal. The mortality of patients with PNP is 75% to 90% [3]. However, a recent study conducted in France [99] revealed a mortality of 51%, 59% and 69% in 1, 2 and 5 years, respectively.

The treatment of PNP to date has been rather disappointing. The skin and mucosal eruptions cause much morbidity and are a frequent cause of death rather than the malignancy itself [100]. The response to therapy is generally poor. In the first place, therapy is aimed at curtailing the production of autoantibodies [101-103]. The proven efficacy therapies include Cyclosporine A [104], Rituximab [1,13,58], Cyclophosphamide [1,67], Mycophenolate mofetil [68]. The most widely suggested specific treatment combines prednisone (0.5-1.0 mg/kg) with cyclosporine (5 mg/kg), and may also include cyclophosphamide (2 mg/kg) [3]. Initially, high-dose corticosteroids form the first line of defense, and are effective to some extent [100]. The addition of steroid-sparing agents, such as azathioprine [100], cyclosporine A [104], and mycophenolate mofetil [68], may reduce steroid intake and thus limit side-effects; however, a high level of caution is advised in patients with paraneoplastic pemphigus and confirmed malignancy, where immunosuppression is paramount and dictates the mainstay of treatment options. Rituximab may be indicated, especially because of association with non-Hodgkin's lymphoma, though there are reports of complications and low therapeutic response [3].

A better prognosis can be expected if the malignancy is less aggressive. This is the case with Castleman's disease and thymoma [7,46]. Early detection and resection of the tumor are essential for the treatment of the patients with castleman's disease. The associated tumors should be resected completely. During the operation, it is important to block the blood supply of the tumor first and to avoid squeezing the tumor during operation. Complete resection is prerequisite for a good prognosis. Using i.v. immunoglobulin before, during and after the operation in a total dose of 1-2 g/kg is recommended to block the circulating autoantibodies released from the tumor, which could cause pulmonary damages [7]. However, except in cases associated to Castleman's disease, treatment of neoplasia is not associated with improvement of PNP in general.

Respiratory failure due to bronchiolitis obliterans is one of the most important causes of death in patients with PNP/PAMS. Pulmonary disease is irreversible and tumor resection or complete response to neoplasia treatment does not alter the progression of respiratory disease [3].

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Conflict of Interest Disclosures

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References

1. Zimmerman J, Bahmer F, Rose C, Zillikens D, Schmidt E (2010) Clinical and immunopathological spectrum of paraneoplastic pemphigus. J Dtsch Dermatol Ges 8: 598-606.

2. Anhalt GJ, Kim SC, Stanley JR, Korman NJ, Jabs DA, et al. (1990) Paraneoplastic pemphigus: An autoimmune mucocutaneous disease associated with neoplasia. N Engl J Med 323: 1729-1735.

3. Porro AM, Caetano Lde V, Maehara Lde S, Enokihara MM (2014) Non-classical forms of pemphigus: pemphigus herpetiformis, gA pemphigus, paraneoplastic pemphigus and IgG/IgA pemphigus. An Bras Dermatol 89: 96-106.

4. Robinson ND, Hashimoto T, Amagai M, Chan LS (1999) The new pemphigus variants. J Am Acad Dermatol 40: 649-671.

5. Choi Y, Nam KH, Lee JB, Lee JY, Ihm CW, et al. (2012) Retrospective analysis of 12 Korean patients with paraneoplastic pemphigus. J Dermatol 39: 973-981.

6. Anhalt GJ (2004) Paraneoplastic pemphigus. J Investig Dermatol Symp Proc 9: 29-33.

7. Zhu X, Zhang B (2007) Paraneoplastic pemphigus. J Dermatol 34: 503-511.

8. Joly P, Richard C, Gilbert D, Courville P, Chosidow O, et al. (2000) Sensitivity and specificity of clinical, histologic, and immunologic features in the diagnosis of paraneopla-stic pemphigus. J Am Acad Dermatol 43: 619-626.

9. Nikolskaia OV, Nousari CH, Anhalt GJ (2003) Paraneoplastic pemphigus in association with Castleman's disease. Br J Dermatol 149: 1143-1151.

10. Sehgal VN, Srivastava G (2009) Paraneoplastic pemphigus/paraneoplastic autoimmune multiorgan syndrome. Int J Dermatol 48: 162-169.

11. Nguyen VT, Ndoye A, Bassler KD, Shultz LD, Shields MC (2001) Classification, clinical manifestations and immunopathological mechanisms of the epithelial variant of paraneoplastic autoimmune multiorgan syndrome. Arch Dermatol 137: 193-206.

12. Gong H, Zhou S, Hu Y, Lan Y, Zeng H, et al. (2016) Recurrent corneal melting in the paraneoplastic pemphigus associated with Castleman's disease. BMC Ophthalmol 16: 106.

13. Vezzoli P, Berti E, Marzano AV (2008) Rationale and efficacy for the use of rituximab in paraneoplastic pemphigus. Expert Rev Clin Immunol 4: 351-364.

14. Ohzono A, Sogame R, Li X, Teye K, Tsuchisaka A, et al. (2015) Clinical and immunological findings in 104 cases of paraneoplastic pemphigus. Br J Dermatol 173: 1447-1452.

15. Nousari HC, Deterding R, Wojtczack H, Aho S, Uitto J, et al. (1999) The mechanism of respiratory failure in paraneoplastic pemphigus. N Engl J Med 340: 1406-1410.

16. Tsuchisaka A, Numata S, Teye K, Natsuaki Y, Kawakami T, et al. (2016) Epiplakin Is a Paraneoplastic Pemphigus Autoantigen and Related to Bronchiolitis Obliterans in Japanese Patients. J Invest Dermatol 136: 399-408.

17. Lee J, Bloom R, Amber KT (2015) A Systematic Review of Patients with Mucocutaneous and Respiratory Complications in Paraneoplastic Autoimmune Multiorgan Syndrome: Castleman's Disease is the Predominant Malignancy. Lung 193: 593-596.

18. Wang R, Li J, Wang M, Hao H, Chen X, et al. (2015) Prevalence of myasthenia gravis and associated autoantibodies in paraneoplastic pemphigus and their correlations with symptoms and prognosis. Br J Dermatol 172: 968-975.

19. Czernik A, Camilleri M, Pittelkow MR, Grando SA (2011) Paraneoplastic autoimmune multiorgan syndrome: 20 years after. Int J Dermatol 50: 905-914.

20. Amagai M, Nishikawa T, Nousari HC, Anhalt GJ, Hashimoto T (1998) Antibodies against desmoglein 3 (pemphigus vulgaris antigen) are present in sera from patients with paraneoplastic pemphigus and cause acantholysis in vivo in neonatal mice. J Clin Invest 102: 775-782.

21. Anzai H, Fujii Y, Nishifuji K, Aoki-Ota M, Ota T, et al. (2004) Conformational epitope mapping of antibodies against desmoglein 3 in experimental murine pemphigus vulgaris. J Dermatol Sci 35: 133-142.

22. Lee SE, Kim SC (2010) Paraneoplastic pemphigus. Dermatol Sin 28: 1-14.

23. Barnadas MA, Curell R, Alomar A, Gelpi C (2009) Paraneoplastic pemphigus with negative direct immunofluorescence in epidermis or mucosa but positive findings in adnexal structures. J Cutan Pathol 36: 34-38.

24. Helou J, Allbritton J, Anhalt GJ (1995) Accuracy of indirect immunofluorescence testing in the diagnosis of paraneoplastic pemphigus. J Am Acad Dermatol 32: 441-447.

25. Yong AA, Tey HL (2013) Paraneoplastic pemphigus. Australas J Dermatol 54: 241-250.

26. Schepens I, Jaunin F, Begre N, Läderach U, Marcus K, et al. (2010) The protease inhibitor alpha-2-macroglobulin-like-1 is the p170 antigen recognized by paraneoplastic pemphigus autoantibodies in human. PLoS One 5: e12250.

27. Kim SC, Kwon YD, Lee IJ, Chang SN, Lee TG (1997) cDNA cloning of the 210-kDa paraneoplastic pemphigus antigen reveals that envoplakin is a component of the antigen complex. J Invest Dermatol 109: 365-369.

28. Mahoney MG, Aho S, Uitto J, Stanley JR (1998) The members of the plakin family of proteins recognized by paraneoplastic pemphigus antibodies include peri-plakin. J Invest Dermatol 111: 308-313.

29. Oursler JR, Labib RS, Ariss-Abdo L, Burke T, O'Keefe EJ, et al. (1992) Human autoantibodies against desmoplakins in paraneoplastic pemphigus. J Clin Invest 89: 1775-1782.

30. Proby C, Fujii Y, Owaribe K, Nishikawa T, Amagai M (1999) Human autoanti-bodies against HD1/plectin in para-neoplastic pemphigus. J Invest Dermatol 112: 153-156.

31. Sanz-Bueno J, Cullen D, Zarco C, Vanaclocha F (2014) Paraneoplastic autoimmune multiorgan syndrome (paraneoplastic pemphigus) with unusual manifestations and without detectable autoantibodies. Indian J Dermatol Venereol Leprol 80: 328-330.

32. Wang J, Zhu X, Li R, Tu P, Wang R, et al. (2005) Paraneoplastic pemphigus associated with Castleman tumor: a commonly reported subtype of paraneoplastic pemphigus in China. Arch Dermatol 141: 1285-1293.

33. Hsiao CJ, Hsu MM, Lee JY, Chen WC, Hsieh WC (2001) Paraneoplastic pemphigus in association with a retroperitoneal Castleman's disease presenting with a lichen planus pemphigoides-like eruption. A case report and review of literature. Br J Dermatol 144: 372-376.

34. Horn TD, Anhalt GJ (1992) Histologic features of paraneoplastic pemphigus. Arch Dermatol 128: 1091-1095.

35. Jing L, Shan Z, Yongchu H, Xixue C, Xuejun Z (2011) Successful treatment of a paraneoplastic pemphigus in a teenager using plasmapheresis, corticosteroids and tumour resection. Clin Exp Dermatol 36: 752-754.

36. Bowen GM, Peters NT, Fivenson DP, Su LD, Nousari HC, et al. (2000) Lichenoid dermatitis in paraneoplastic pemphigus: a pathogenic trigger of epitope spreading? Arch Dermatol 136: 652-656.

37. Wen X, Jiang X (2012) Paraneoplastic pemphigus in association with Castleman disease of the pararenal retroperitoneum. J Dermatol 39: 662-664.

38. Kim SC, Chang SN, Lee IJ, Park SD, Jeong ET, et al. (1998) Localized mucosal involvement and severe pulmonary involvement in a young patient with paraneoplastic pemphigus associated with Castleman's tumour. Br J Dermatol 138: 667-671.

39. Lemon MA, Weston WL, Huff JC (1997) Childhood paraneoplastic pemphigus associated with Castleman's tumour. Br J Dermatol 136: 115-117.

40. Jansen T, Plewig G, Anhalt GJ (1995) Paraneoplastic pemphigus with clinical features of erosive lichen planus associated with Castleman's tumor. Dermatology 190: 245-250.

41. Wolff H, Kunte C, Messer G, Rappersberger K, Held E, et al. (1999) Paraneoplastic pemphigus with fatal pulmonary involvement in a woman with a mesenteric Castleman tumour. Br J Dermatol 140: 313-316.

42. Lee IJ, Kim SC, Kim HS, Bang D, Yang WI, et al. (1999) Paraneoplastic pemphigus associated with follicular dendritic cell sarcoma arising from Castleman's tumor. J Am Acad Dermatol 40: 294-297.

43. Tey HL, Tang MB (2009) A case of paraneoplastic pemphigus associated with Castleman's disease presenting as erosive lichen planus. Clin Exp Dermatol 34: e754-e756.

44. Jindal T, Meena M, Kumar A, Khaitan BK (2011) Paraneoplastic pemphigus with Castleman's disease and bronchiolitis obliterans. Pediatr Int 53: 1108-1109.

45. Chorzelski T, Hashimoto T, Maciejewska B, Amagai M, Anhalt GJ, et al. (1999) Paraneoplastic pemphigus associated with Castleman tumor, myasthenia gravis and bronchiolitis obliterans. J Am Acad Dermatol 41: 393-400.

46. Jun Zhang, Qi-lu Qiao, Xi-xue Chen, Ping Liu, Jian-xing Qiu, et al. (2011) Improved outcomes after complete resection of underlying tumors for patients with paraneoplastic pemphigus: a single-center experience of 22 cases. J Cancer Res Clin Oncol 137: 229-234.

47. Marzano AV, Vezzoli P, Mariotti F (2005) Paraneoplastic pemphigus associated with follicular dendritic cell sarcoma and Castleman disease. Br J Dermatol 153: 214-215.

48. Daneshpazhooh M, Moineddin F, Kiani A, Naraghi ZS, Firooz A, et al. (2012) Fatal paraneoplastic pemphigus after removal of Castleman's disease in a child. Pediatr Dermatol 29: 656-657.

49. AV Marzano, A Grammatica, E Cozzani, M Terracina, E Berti (2001) Paraneoplastic pemphigus. A report of two cases associated with chronic B-cell lymphocytic leukaemia. Br J Dermatol 145: 127-131.

50. Wind LJ, van der Velden AW, Diercks GF, Pas HH, Jonkman MF (2010) Paraneoplastic pemphigus in a patient with non-Hodgkin lymphoma. Ned Tijdschr Geneeskd 154: 2183.

51. Ishii N, Hashimoto T (2008) A case of paraneoplastic pemphigus who shifted to pemphigus vulgaris. J Eur Acad Dermatol Venereol 22: 374-375.

52. Hayanga AJ, Lee TM, Pannucci CJ, Knipp BS, Olsen SH, et al. (2010) Paraneoplastic pemphigus in a burn intensive care unit: case report and review of the literature. J Burn Care Res 31: 826-829.

53. Ishigami T, Kubo Y, Matsudate Y, Ansai S, Arase S, et al. (2011) Paraneoplastic pemphigus associated with non-Hodgkin's lymphoma. Eur J Dermatol 21: 122-124.

54. Fried R, Lynfield Y, Vitale P, Anhalt G (1993) Paraneoplastic pemphigus appearing as bullous pemphigoid-like eruption after palliative radiation therapy. J Am Acad Dermatol 29: 815-817.

55. Tilakaratne W, Dissanayake M (2005) Paraneoplastic pemphigus: a case report and review of literature. Oral Dis 11: 326-329.

56. Batista MD, Takano D, Lopes RD, Enokihara MM, Michalany NS, et al. (2008) Paraneoplastic pemphigus associated with non-Hodgkin lymphoma. Dermatol Online J 14: 11.

57. Krogel C, Fischer T, Heidel F (2010) Severe paraneoplastic pemphigus in a patient with follicular lymphoma. Eur J Haematol 84: 365.

58. Heizmann M, Itin P, Wernli M, Borradori L, Bargetzi MJ (2001) Successful treatment of paraneoplastic pemphigus in follicular NHL with rituximab: report of a case and review of treatment for paraneoplastic pemphigus in NHL and CLL. Am J Hematol 66: 142-144.

59. Joly P, Thomine E, Gilbert D, Verdier S, Delpech A, et al. (1994) Overlapping distribution of autoantibody specificities in paraneoplastic pemphigus and pemphigus vulgaris. J Invest Dermatol 103: 65-72.

60. Vun YY, Lun K, Strutton G (2004) Use of biosynthetic dressings in paraneoplastic pemphigus. Australas J Dermatol 45: 133-135.

61. Rossum MM, Verhaegen NT, Jonkman MF, MA Mackenzie, A Koster, et al. (2004) Follicular non-Hodgkin's lymphoma with refractory paraneoplastic pemphigus: case report with review of novel treatment modalities. Leukemia & Lymphoma 45: 2327-2332.

62. Stark GL, Goff DK, Spickett GP, Wojnarowska F, Langtry JA (2003) Paraneoplastic pemphigus occuring after radiotherapy for relapsed non-Hodgkin's lymphoma in a patient with common variable immunodeficiency. Hematol J 4: 154-158.

63. Martinez De Pablo MI, Iranzo P, Mascaro JM, Llambrich A, Baradad M, et al. (2005) Paraneoplastic pemphigus associated with non-Hodgkin B-cell lymphoma and good response to prednisone. Acta Derm Venereol 85: 233-235.

64. Ekbäck M, Uggla B (2012) Paraneoplastic pemphigus associated with chronic lymphocytic leukaemia: treatment with alemtuzumab. Leuk Res 36: e190-e191.

65. Izaki S, Yoshizawa Y, Kitamura K, Kato H, Hashimoto H, et al. (1996) Paraneoplastic pemphigus: potential therapeutic effect of plasmapheresis. Br J Dermatol 134: 987-989.

66. Yan Z, Hua H, Gao Y (2010) Paraneoplastic pemphigus characterized by polymorphic oral mucosal manifestations-report of two cases. Quintessence Int 41: 689-694.

67. Nousari HC, Brodsky RA, Jones RJ, Grever MR, Anhalt GJ (1999) Immunoablative high-dose cyclophosphamide without stem cell rescue in paraneoplastic pemphigus: report of a case and review of this new therapy for severe autoimmune disease. J Am Acad Dermatol 40: 750-754.

68. Williams JV, Marks JG Jr, Billingsley EM (2000) Use of mycophenolate mofetil in the treatment of paraneoplastic pemphigus. Br J Dermatol 142: 506-508.

69. van Mook WNK, Fickers MM, Theunissen PH, van der Kley JA, Duijvestijn JA, et al. (2001) Paraneoplastic pemphigus as the initial presentation of chronic lymphocytic leukemia. Ann Oncol 12: 115-118.

70. Powell AM, Albert S, Oyama N, Y Sakuma-Oyama, B Bhogal, et al. (2004) Paraneoplastic pemphigus secondary to fludarabine evolving into unusual oral pemphigus vegetans. J Eur Acad Dermatol Venereol 18: 360-364.

71. Bronnimann M, von Felbert V, Streit M, T Hunziker, LR Braathen (2004) Progressive respiratory failure in paraneoplastic pemphigus associated with chronic lymphocytic leukemia. Dermatology 208: 251-254.

72. Wang J, Bu DF, Li T, Zheng R, Zhang BX, et al. (2005) Autoantibody production from a thymoma and a follicular dendritic cell sarcoma associated with paraneoplastic pemphigus. Br J Dermatol 153: 558-564.

73. Lee SE, Hashimoto T, Kim SC (2008) No mucosal involvement in a patient with paraneoplastic pemphigus associated with thymoma and myasthenia gravis. Br J Dermatol 159: 986-988.

74. Barbetakis N, Samanidis G, Paliouras D, Boukovinas I, Asteriou C, et al. (2008) Paraneoplastic pemphigus regression after thymoma resection. World J Surg Oncol 6: 83.

75. Leyn J, Degreef H (2001) Paraneoplastic pemphigus in a patient with a thymoma. Dermatology 202: 151-154.

76. Ishii N, Hamada T, Koga H, Sogame R, Ohyama B, et al. (2012) Decline of disease activity and autoantibodies to desmoglein 3 and envoplakin by oral prednisolone in paraneoplastic pemphigus with benign thymoma. Eur J Dermatol 22: 547-549.

77. Norris DL, Saywell MS, Strutton GM, Stephenson GJ (1993) Pemphigus vulgaris associated with spindle cell thymoma. Australas J Dermatol 34: 97-102.

78. Becker LR, Bastian BC, Wesselmann U, Karl S, Hamm H, et al. (1998) Paraneoplastic pemphigus treated with dexamethasone/cyclophosphamide pulse therapy. Eur J Dermatol 8: 551-553.

79. Kirsner RS, Anhalt GJ, Kerdel FA (1995) Treatment with alpha interferon associated with the development of paraneoplastic pemphigus. Br J Dermatol 132: 474-478.

80. Perniciaro C, Kuechle MK, Colon-Otero G, Raymond MG, Spear KL, et al. (1994) Paraneoplastic pemphigus: a case of prolonged survival. Mayo Clin Proc 69: 851-855.

81. Perera GK, Devereux S, Mufti G, Salisbury J, Creamer D (2005) PNP with Waldenstrom's macroglobulinaemia. Clin Exp Dermatol 30: 27-29.

82. Anhalt GJ (2001) Paraneoplastic pemphigus. the role of tumours and drugs. Br J Dermatol 144: 1102-1104.

83. Choh NA, Qayoom S, Shaheen F, Malik RA, Rabbani I, et al. (2014) Retroperitoneal Castlemans disease associated with paraneoplastic pemphigus. Hematol Oncol Stem Cell Ther 7: 93-96.

84. Pfistershammer K, Minimair G, Födinger D, Czerny M, Zauner C, et al. (2009) Fatal paraneoplastic pemphigus associated with a mediastinal tumor. J Dtsch Dermatol Ges 7: 356-359.

85. Lee SE, Kim HR, Hashimoto T, Kim SC (2008) Paraneoplastic pemphigus developed shortly after resection of follicular dendritic cell sarcoma. Acta Derm Venereol 88: 410-412.

86. Schoen H, Foedinger D, Derfler K, G Amann, K Rappersberger, et al. (1998) Immunoapheresis in paraneoplastic pemphigus. Arch Dermatol 134: 706-710.

87. van der Waal RI, Pas HH, Nousari HC, Schulten EA, Jonkman MF, et al. (2000) Paraneoplastic pemphigus caused by an epithelioid leiomyosarcoma and associated with fatal respiratory failure. Oral Oncol 36: 390-393.

88. Krunic AL, Kokai D, Bacetic B, Kesic V, Nikolic MM, et al. (1997) Retroperitoneal round-cell liposarcoma associated with paraneoplastic pemphigus presenting as lichen planus pemphigoideslike eruption. Int J Dermatol 36: 526-529.

89. Beele H, Claerhout I, Kestelyn P, Dierckxens L, Naeyaert JM, et al. (2001) Bilateral corneal melting in a patient with paraneoplastic pemphigus. Dermatology 202: 147-150.

90. Santi CG, Flores RS, Medina MM, Maruta CW, Aoki V, et al. (2005) Paraneoplastic pemphigus associated with pelvic inflammatory fibrosarcoma: a case report. J Dermatol 32: 1014-1020.

91. Berg WA, Fishman EK, Anhalt GJ (1993) Retroperitoneal reticulum cell sarcoma: a cause of paraneoplastic pemphigus. South Med J 86: 215-217.

92. H Schaeppi, JW Bauer, R Hametner, D Metze, S Ortiz-Urda, et al. (2001) A localized variant of paraneoplastic pemphigus: acantholysis associated with malignant melanoma. Br J Dermatol 144: 1249-1254.

93. Rongioletti F, Truchetet F, Rebora A (1993) Paraneoplastic pemphigoid-pemphigus? Subepidermal bullous disease with pemphigus-like direct immunofluorescence. Int J Dermatol 32: 48-51.

94. Martel P, Gilbert D, Labeille B, J Kanitakis, P Joly (2000) A case of paraneoplastic pemphigus with antidesmoglein 1 antibodies as determined by immunoblotting. British Journal of Dermatology 142: 812-813.

95. Mignogna MD, Fortuna G, Leuci S, Adamo D, Ruoppo E (2009) Metastatic prostate cancer presenting as paraneoplastic pemphigus: a favourable clinical response to combined androgen blockade and conventional immunosuppressive therapy. Br J Dermatol 160: 468-470.

96. Kubota Y, Yoshino Y, Mizoguchi M (1994) A case of herpetiform pemphigus associated with lung cancer. J Dermatol 21: 609-611.

97. Prado R, Brice SL, Fukuda S, Hashimoto T, Fujita M (2011) Paraneoplastic pemphigus herpetiformis with IgG antibodies to desmoglein 3 and without mucosal lesions. Arch Dermatol 147: 67-71.

98. Ghandi N, Ghanadan A, Azizian MR, Hejazi P, Aghazadeh N, et al. (2015) Paraneoplastic pemphigus associated with inflammatory myofibroblastic tumour of the mediastinum: A favourable response to treatment and review of the literature. Australas J Dermatol 56: 120-123.

99. Leger S, Picard D, Ingen-Housz-Oro S, Arnault JP, Aubin F, et al. (2012) Prognostic factors of paraneoplastic pemphigus. Arch Dermatol 148: 1165-1172.

100. Camisa C, Helm TN (1993) Paraneoplastic pemphigus is a distinct neoplasia-induced autoimmune disease. Arch Dermatol 129: 883-886.

101. Loo WJ, Burrows NP (2004) Management of autoimmune skin disorders in the elderly. Drugs Aging 21: 767-777.

102. Grando SA (2004) New approaches to the treatment of pemphigus. J Invest Dermatol Symp Proc 9: 84-91.

103. Hayag MV, Cohen JA, Kerdel FA (2000) Immunoablative high-dose cyclophosphamide without stem cell rescue in a patient with pemphigus vulgaris. J Am Acad Dermatol 43: 1065-1069.

104. Gergely L, Varoczy L, Vadasz G, Remenyik E, Illés A (2003) Successful treatment of B cell chronic lymphocytic leukemia-associated severe paraneoplastic pemphigus with cyclosporin A. Acta Haematol 109: 202-205.