Paraneoplastic pemphigus: A trait d’union between dermatology and oncology
Dario Didona1, Biagio Didona1, Antonio G. Richetta2, Carmen Cantisani2, Elisa Moliterni2, Stefano Calvieri2, Giovanni Paolino2*

1 Hospitalization and Health Care, (IRCCS) Istituto Dermopatico dell’Immacolata, Via Monti di Creta, Rome, Italy
2 Clinica Dermatologica, La Sapienza University of Rome, Viale del Policlinico 15, Rome, Italy

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

Citation: Didona D, Didona B, Richetta AG, et al. Paraneoplastic pemphigus: A trait d’union between dermatology and oncology. Adv Mod Oncol Res 2015; 1(2): 97–103; http://dx.doi.org/10.18282/amor.v1.i2.42

*Correspondence to: Giovanni Paolino, Clinica Dermatologica, La Sapienza University of Rome, Viale del Policlinico 15, 00186, Rome, Italy, gio8519@libero.it.

Received: 14th September 2015; Accepted: 16th October 2015; Published Online: 3rd December 2015

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 auto-antibodies 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.

Copyright © 2015 Didona D, et al. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License (http://creativecommons.org/licenses/by-nc/4.0/), permitting all non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.
Paraneoplastic pemphigus: A trait d'union between dermatology and oncology

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 [37,38]. 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 [3,42,43]. 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 [51,38,40]. 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 [16,38]. 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...
PNP\textsuperscript{[46]}. PNP can also involve the respiratory epithelium in 59.1%–92.8% of cases\textsuperscript{[8,36]}, causing dyspnea, obstructive lung disease and bronchiolitis obliterans, which may be fatal\textsuperscript{[6,47]}. However, the pulmonary involvement affects mainly children and Chinese patients with Castleman’s disease\textsuperscript{[40,47]}. Usually, a neoplasm is detected before the onset of PNP\textsuperscript{[4,38–40]}. However, in about 30% of cases PNP, the clinical manifestation leads to the detection of an occult tumor\textsuperscript{[36,38]}.

**Histological features**

The pathological findings vary with the clinical features\textsuperscript{[4,30]}. On one hand, suprabasal acantholysis with scattered inflammatory infiltrates could be detected in presence of blisters (Figure 3\textsuperscript{[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\textsuperscript{[30,35]}. Lesions with a mixed clinical feature might show concomitant acantholysis occurring with lichenoid interface dermatitis\textsuperscript{[30,38,40]}.

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

**Immunological studies**

Direct immunofluorescence (DIF) usually shows IgG and/or C3 deposition in the epidermal intercellular spaces (EIS) alone\textsuperscript{[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\textsuperscript{[48]}. In addition, linear deposits of IgG or C3 in the basement membrane zone could be detected\textsuperscript{[30]}. This pattern could be a clue to differentiate PNP from other forms of pemphigus, in which Ig deposits are detected only between keratinocytes\textsuperscript{[31]}. However, DIF is found to be negative in approximately 50% of the cases\textsuperscript{[48]}. False negatives are commonly due to necrotic tissue (especially in mucosal biopsies) and the lichenoid clinical pattern of some lesions\textsuperscript{[35,48]}.

![Figure 4 Positive indirect immunofluorescence on rat urinary bladder epithelium](image)

Indirect immunofluorescence (IIF) could be performed on different substrates, including normal human skin, rat bladder (Figure 4), rat myocardium, rat lung, and monkey esophagus\textsuperscript{[48]}. IIF detects autoantibodies to plakins; among them, autoantibodies to envoplakin and periplakin are the most specific\textsuperscript{[40]}. 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\textsuperscript{[38,49]}. Furthermore, IIF on rat bladder has shown a high specificity (83%)\textsuperscript{[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\textsuperscript{[49-51]}.

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\textsuperscript{[52]}. However, there were also PNP patients without anti-DSG autoantibodies described in the literature\textsuperscript{[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%\textsuperscript{[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\textsuperscript{[54]}. Immunoprecipitation (IP) has been considered as the gold standard for the diagnosis of PNP\textsuperscript{[55]}. IP can show antibodies against several epidermal antigens, including plakin family and A2ML1\textsuperscript{[31]}. In addition, a positive IP test is a major criterion for the diagnosis of PNP\textsuperscript{[56]}. Immunoblotting (IB) has been used to detect antibodies against desmopla kin I and II, periplakin, and envoplakin on normal human keratinocytes extracts\textsuperscript{[30,48]}.
Diagnosis

According to Anhalt et al., the diagnostic criteria include 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 sensitivity\[48,49\]. 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 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 mucosa                  |
|           | 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                                  |

ELISA is useful to formulate a correct diagnosis\[57\]. Furthermore, the link between anti-DSG-3 antibodies and bronchiolitis obliterans (BO)\[65\] 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\[38-40\].

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\[31\], 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\[38\].
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\cite{Anhalt2004, Vassileva2014, Czernik2011, Yong2013, Lee2013}. It has also been suggested to use perioperative intravenous immunoglobulins to block the release of autoantibodies during excision\cite{Yong2013}. 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\cite{Anhalt2004, Vassileva2014, Czernik2011, Yong2013, Lee2013}.

Early antimicrobial therapy is recommended to reduce the risk of sepsis due to loss of skin integrity and immunosuppressive therapy\cite{Cervini2010}. Antalgic therapy is thought to be useful in reducing the pain linked to extensive mucosal erosions\cite{Yong2013}.

**Prognosis**

The prognosis of PNP is generally poor, with a staggering 90% mortality rate\cite{Anhalt1990, Czernik2011, Cervini2010}. The death is usually caused by severe complications including sepsis, gastrointestinal bleedings and BO\cite{Anhalt1990, Czernik2011, Cervini2010}. At this regard, a link between anti-DSG-3 antibodies and BO has been reported\cite{Matz1997}. 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\cite{Cervini2010, Czernik2011, Yong2013}. In fact, PNP lesions generally progress even if malignancy is removed or under controlled\cite{Cervini2010, Czernik2011, Yong2013}. 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\cite{Mimouni2002}. 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\cite{Dong2008}.

**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.

**References**

1. Anhalt GJ, Kim SC, Stanley JR, et al. Paraneoplastic pemphigus. An autoimmune mucocutaneous disease associated with neoplasia. N Engl J Med 1990; 323(25): 1729–1735.

2. Sehgal VN, Srivastava G. Paraneoplastic pemphigus/paraneoplastic autoimmune multiorgan syndrome. Int J Dermatol 2009; 48(2): 162–169.

3. Nguyen VT, Ndoye A, Bassler KD, et al. Classification, clinical manifestations, and immunopathological mechanisms of the epithelial variant of paraneoplastic autoimmune multiorgan syndrome: a reappraisal of paraneoplastic pemphigus. Arch Dermatol 2001; 137(2): 193–206.

4. Anhalt GJ. Paraneoplastic pemphigus. J Invest Dermatol Symp Proc 2004; 9(1): 29–33.

5. Vassileva S, Drenovska K, Manuelyan K. Autoimmune blistering dermatoses as systemic diseases. Clin Dermatol 2014; 32(3): 364–375.

6. Czernik A, Camilleri M, Pittelkow MR, et al. Paraneoplastic autoimmune multiorgan syndrome: 20 years after. Int J Dermatol 2011; 50(8): 905–914.

7. Ogawa H, Sakuma M, Morioka S, et al. The incidence of external malignancies in pemphigus and bullous pemphigoid in Japan. J Dermatol Sci 1995; 9(2): 135–141.

8. Cervini AB, Tosi V, Kim SH, et al. Paraneoplastic pemphigus or paraneoplastic autoimmune multiorgan syndrome. Report of 2 cases in children and a review of the literature. Actas Dermosifiliogr 2010; 101(10): 879–886.

9. Mimouni D, Anhalt GJ, Lazarova Z, et al. Paraneoplastic pemphigus in children and adolescents. Br J Dermatol 2002; 147(4): 725–732.

10. Lane JE, Woody C, Davis LS, et al. Paraneoplastic autoimmune multiorgan syndrome (paraneoplastic pemphigus) in a child: case report and review of the literature. Pediatrics 2004; 114(4): 513–516.

11. Yong AA, Tey HL. Paraneoplastic pemphigus. Australas J Dermatol 2013; 54(4): 241–250.

12. Bowen GM, Peters NT, Fivenson DP, et al. Lichenoid dermatitis in paraneoplastic pemphigus: a pathogenic trigger of epitope spreading? Arch Dermatol 2000; 136(5): 652–656.

13. Matz H, Milner Y, Frusic-Zlotkin M, et al. Paraneoplastic pemphigus associated with pancreatic carcinoma. Acta Derm Venereol 1997; 77(4): 289–291.

14. Wong KC, Ho KK. Pemphigus with pemphigoid-like presentation, associated with squamous cell carcinoma of the tongue. Australas J Dermatol 2000; 41(3): 178–180.

15. Lee JJ, Kim SC, Kim HS, et al. Paraneoplastic pemphigus associated with follicular dendritic cell sarcoma arising
Paraneoplastic pemphigus: A trait d’union between dermatology and oncology

from Castleman’s tumor. J Am Acad Dermatol 1999; 40(2 Pt 2): 294–297.
16. VanderWaal RI, Pas HH, Anhalt GJ, et al. PNP as the presenting symptom of lymphoma of the tongue. Oral Oncol 1998; 34(6): 567–570.
17. Schaeppi H, Bauer JW, Hametner R, et al. Localized variant of paraneoplastic pemphigus: acantholysis associated with malignant melanoma. Br J Dermatol 2001; 144(6): 1249–1254.
18. Bazarbachi A, Bachelez H, Dehen L, et al. Lethal paraneoplastic pemphigus following treatment of chronic lymphocytic leukaemia with fludarabine. Ann Oncol 1995; 6(7): 730–731.
19. Anhalt GJ. Paraneoplastic pemphigus: the role of tumours and drugs. Br J Dermatol 2001; 144(6): 1102–1104.
20. Lee MS, Kossard S, Ho KK, et al. Paraneoplastic pemphigus triggered by radiotherapy. Australas J Dermatol 1995; 36(4): 206–210.
21. Martel P, Loiseau P, Joly P, et al. Paraneoplastic pemphigus is associated with the DRB1*03 allele. J Autoimmun 2003; 20(1): 91–95.
22. Liu Q, Bu DF, Li D, et al. Genotyping of HLA-I and HLA-II alleles in Chinese patients with paraneoplastic pemphigus. Br J Dermatol 2008; 158(3): 587–591.
23. Kiyokawa C, Ruhrberg C, Nie Z, et al. Envoplakin and periliplakin are components of the paraneoplastic pemphigus antigen complex. J Invest Dermatol 1998; 111(6): 1236–1238.
24. Kim SC, Kwon YD, Lee IJ, et al. cDNA cloning of the 210-kDa paraneoplastic pemphigus antigen reveals that envoplakin is a component of the antigen complex. J Invest Dermatol 1997; 109(3): 365–369.
25. Oursler JR, Labib RS, Ariss-Abdo L, et al. Human autoantibodies against desmoplakin in paraneoplastic pemphigus. J Clin Invest 1992; 89(6): 1775–1782.
26. Borradori L, Trueb RM, Jaunin F, et al. Autoantibodies from a patient with paraneoplastic pemphigus bind perilakin, a novel member of the plakin family. J Invest Dermatol 1998; 111(2): 338–340.
27. Lambert J, Bracke S, van Roy F, et al. Serum plakophilin-3 autoreactivity in paraneoplastic pemphigus. Br J Dermatol 2010; 163(3): 630–632.
28. Brandt O, Rafei D, Podstawa E, et al. Differential IgG recognition of desmoglein 3 by paraneoplastic pemphigus and pemphigus vulgaris sera. J Invest Dermatol 2012; 132(6): 1738–1741.
29. Amagai M, Nishikawa T, Nousari HC, et al. 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 1998; 102(4): 775–782.
30. Zimmermann J, Bahmer F, Rose C, et al. Clinical and immunopathological spectrum of paraneoplastic pemphigus. J Dtsch Dermatol Ges 2010; 8(8): 598–606.
31. Numata S, Teye K, Tsuruta D, et al. Anti-alpha-2-macroglobulin-like-1 autoantibodies are detected frequently and may be pathogenic in paraneoplastic pemphigus. J Invest Dermatol 2013; 133(7): 1785–1793.
32. Schepens I, Jaunin F, Begre N, et al. The protease inhibitor alpha-2-macroglobulin-like-1 is the p170 antigen recognized by paraneoplastic pemphigus autoantibodies in human. PLoS One 2010; 5(8): e12250.
33. Billet SE, Grando SA, Pittelkow MR. Paraneoplastic autoimmune multiorgan syndrome: review of the literature and support for a cytotoxic role in pathogenesis. Autoimmunity 2006; 39(7): 617–630.
34. Reich K, Brinck U, Letschert M, et al. Graft-versus-host disease-like immunophenotype and apoptotic keratinocyte death in paraneoplastic pemphigus. Br J Dermatol 1999; 141(4): 739–746.
35. Cummins DL, Mimouni D, Tzu J, et al. Lichenoid paraneoplastic pemphigus in the absence of detectable antibodies. J Am Acad Dermatol 2007; 56(1): 153–159.
36. Wade MS, Black MM. Paraneoplastic pemphigus: a brief update. Australas J Dermatol 2005; 46: 1–8.
37. Bialy-Golan A, Brenner S, Anhalt GJ. Paraneoplastic pemphigus: oral involvement as the sole manifestation. Acta Derm Venereol 1996; 76(3): 253–254.
38. Lee SE, Kim SC. Paraneoplastic pemphigus. Dermatol Sin 2010; 28(1): 1–14.
39. Vassileva S, Drenovska K, Manuelyan K. Autoimmune blistering dermatoses as systemic diseases. Clin Dermatol 2014; 32(3): 364–375.
40. Zhu X, Zhang B. Paraneoplastic pemphigus. J Dermatol 2007; 34(8): 503–511.
41. Lee SE, Hashimoto T, Kim SC. No mucosal involvement in a patient with paraneoplastic pemphigus associated with thymoma and myasthenia gravis. Br J Dermatol 2008; 159(4): 986–988.
42. Meyers SJ, Varley GA, Meisler DM, et al. Conjunctival involvement in paraneoplastic pemphigus. Am J Ophthalmol 1992; 114(5): 621–624.
43. Ng PP, Rencic A, Nousari HC. Paraneoplastic pemphigus: a refractory autoimmune mucocutaneous disease. J Cutan Med Surg 2002; 6(5): 434–437.
44. Mutasim DF, Pelc NJ, Anhalt GJ. Paraneoplastic pemphigus. Dermatol Clin 1993; 11(3): 473–481.
45. Tankel M, Tannenbaum S, Parekh S. Paraneoplastic pemphigus presenting as an unusual bullous eruption. J Am Acad Dermatol 1993; 29(5 Pt 2): 825–858.
46. Sapadin AN, Anhalt GJ. Paraneoplastic pemphigus with a pemphigus vegetans-like plaque as the only cutaneous

doi: 10.18282/amor.v1.i2.42
manifestation. J Am Acad Dermatol 1998; 39(5 Pt 2): 867–871.

47. Maldonado F, Pittelkow MR, Ryu JH. Constrictive bronchiolitis associated with paraneoplastic autoimmune multi-organ syndrome. Respiratory Medicine 2009; 14(1): 129–133.

48. Joly P, Richard C, Gilbert D, et al. Sensitivity and specificity of clinical, histologic, and immunologic features in the diagnosis of paraneoplastic pemphigus. J Am Acad Dermatol 2000; 43(4): 619–626.

49. Helou J, Allbritton J, Anhalt G. Accuracy of indirect immunofluorescence in the diagnosis of paraneoplastic pemphigus. J Am Acad Dermatol 1995; 32(3): 441–447.

50. Cozzani E, Dal Bello MG, Mastrogiacomo A, et al. Antidesmoplakin antibodies in pemphigus vulgaris. Br J Dermatol 2006; 154(4): 624–628.

51. Kazeroonian S, Mahoney MG, Uitto J, et al. Envelopplakin and periplakin, the paraneoplastic pemphigus antigens, are also recognized by pemphigus foliaceus autoantibodies. J Invest Dermatol 2000; 115(3): 505–507.

52. Ishii N, Maeyama Y, Karashima T, et al. Immunoserological analyses of 55 patients with pemphigus at the Dermatological Department of Kurume University Hospital: an 11-year retrospective study (1996–2006). Int J Dermatol 2008; 47(12): 1321–1322.

53. Probst C, Schlumberger W, Stöcker W, et al. Development of ELISA for the specific determination of autoantibodies against envelopplakin and periplakin in paraneoplastic pemphigus. Clin Chim Acta 2009; 410(1-2): 13–18.

54. Ishii N, Teye K, Fukuda S, et al. Anti-desmocollin autoantibodies in nonclassical pemphigus. Br J Dermatol 2015 Jul; 3(1): 59–68.

55. Hashimoto T, Amagai M, Watanabe K, et al. Characterization of paraneoplastic pemphigus autoantigens by immunoblot analysis. J Invest Dermatol 1995; 104(5): 829–834.

56. Camisa C, Helm TN. Paraneoplastic pemphigus is a distinct neoplasia-induced autoimmune disease. Arch Dermatol 1993; 129(7): 883–886.

57. Ohzono A, Sogame R, Li X, et al. Clinical and immunological findings in 104 cases of paraneoplastic pemphigus. Br J Dermatol 2015 Sep 10. doi: 10.1111/bjd.14162. [Epub ahead of print]

58. Hata T, Nishimoto S, Nagao K, et al. Ectopic expression of epidermal antigens renders the lung a target organ in paraneoplastic pemphigus. J Immunol 2013; 191(1): 83–90.

59. Poot AM, Diercks GF, Kramer D, et al. Laboratory diagnosis of paraneoplastic pemphigus. Br J Dermatol 2013; 169(5): 1016–1024.

60. Dega H, Laporte JL, Joly P, et al. Paraneoplastic pemphigus associated with Hodgkin’s disease. Br J Dermatol 1998; 138(1): 196–198.

61. Martinez De Pablo MI, Iranzo P, et al. Paraneoplastic pemphigus associated with non-Hodgkin B-cell lymphoma and good response to prednisone. Acta Derm Venereol 2005; 85(3): 233–235.

62. Gergely L, Váróczy L, Vadász G, et al. Successful treatment of B cell chronic lymphocytic leukemia-associated severe paraneoplastic pemphigus with cyclosporin A. Acta Haematol 2003; 109(4): 202–205.

63. Williams JV, Marks JG, Billingsley EM. Use of mycophenolate mofetil in the treatment of paraneoplastic pemphigus. Br J Dermatol 2000; 142(3): 506–508.

64. Hertzberg MS, Schifer M, Sullivan J, et al. Paraneoplastic pemphigus in two patients with B-cell non-Hodgkin’s lymphoma: significant responses to cyclophosphamide and prednisolone. Am J Hematol 2000; 63(2): 105–106.

65. Hayag MV, Cohen JA, Kerdel FA. Immunoablative high-dose cyclophosphamide without stem cell rescue in a patient with pemphigus vulgaris. J Am Acad Dermatol 2000; 43(6): 1065–1069.

66. Tan-Lim R, Bystryn JC. Effect of plasmapheresis therapy on circulating levels of pemphigus antibodies. J Am Acad Dermatol 1990; 22(1): 35–40.

67. Izaki S, Yoshizawa Y, Kitamura K, et al. Paraneoplastic pemphigus: potential therapeutic effect of plasmapheresis. Br J Dermatol 1996; 134(5): 987–989.

68. Hertl M, Zillikens D, Borradori L, et al. Recommendations for the use of rituximab (anti-CD20 antibody) in the treatment of autoimmune bullous skin diseases. J Dtsch Dermatol Ges 2008; 6(5): 366–373.

69. Hainsworth JD, Burris HA, Morrissey LH, et al. Rituximab monoclonal antibody as initial systemic therapy for patients with low-grade non-Hodgkin’s lymphoma. Blood 2000; 95(10): 3052–3056.

70. Hohwy T, Bang K, Steiniche T, et al. Alemtuzumab-induced remission of both severe paraneoplastic pemphigus and leukemic bone marrow infiltration in a case of treatment-resistant B-cell chronic lymphocytic leukemia. Eur J Haematol 2004; 73(3): 206–209.

71. Wang J, Zhu X, Li R, et al. Paraneoplastic pemphigus associated with Castleman tumor: a commonly reported subtype of paraneoplastic pemphigus in China. Arch Dermatol 2005; 141(10): 1285–1293.

72. Dong Y, Wang M, Nong L, et al. Clinical and laboratory characterization of 114 cases of Castleman disease patients from a single centre: paraneoplastic pemphigus is an unfavourable prognostic factor. Br J Haematol 2015; 169(6): 834–842.