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Desmosomes in disease: a guide for clinicians.

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40 ABSTRACT

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42 **The large number of diseases occurring when desmosome constituents are**
43 **impaired provides striking evidence for the key role of desmosomes in**
44 **maintaining tissue integrity. A detailed understanding of the molecular**
45 **alterations causing desmosomal dysfunction has, in turn, underpinned the**
46 **development of novel diagnostic tools. This has salient clinical implications for**
47 **dentists and oral medicine practitioners because the majority of desmosomal**
48 **diseases affects the oral cavity. In the present article, we review the autoimmune,**
49 **infectious, genetic, and neoplastic diseases that target the desmosome, with**
50 **particular emphasis on clinical manifestations, diagnostic pathways and relevant**
51 **laboratory investigations.**

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55 **Running head:** Diseases of the desmosome

56 **Key words:** desmosome, pemphigus, blistering diseases
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Giulio Bizzozero, an Italian pathologist, was the first to sketch and describe what would later be called “desmosome” (Bizzozero, 1864). One hundred and fifty years later, vast knowledge has accumulated on the complex biochemical structure and role of the desmosome in health and disease. To date, approximately 30 different conditions including infectious, autoimmune, genetic and neoplastic diseases are known to involve desmosomal dysfunction. This review presents an update on desmosome pathophysiology, particularly for clinicians involved in the diagnosis of muco-cutaneous diseases.

Molecular composition and ultrastructure of the desmosome: the basics

Desmosomes, along with the adherens junctions (AJs), gap junctions and tight junctions (TJs), are the predominant type of adhesive intercellular junctions in vertebrate tissues, particularly those requiring strength, extensibility, and elasticity such as epithelium. It is now well established that desmosomes are dynamic structures with unique plasticity. Their ability to switch between hyper-adhesive and unordered states is essential to maintain tissue integrity and homeostasis.

At the ultrastructural level, desmosomes appear as multi-layered symmetrical disc-shaped structures of 0.2-0.5 μm in diameter found between cellular membranes of adjacent cells. These organelles link keratin intermediate filaments (KIFs) to the plasma membrane region and morphologically consist of a central electron-dense midline between two plasma membranes (desmoglea) and intracellular dense plaques, i.e. the outer and inner dense plaques. The extracellular portion forming the desmoglea contains desmosomal cadherins desmogleins (Dsg1-4) and desmocollins (Dsc1-3). These calcium-dependent proteins are expressed in a tissue-specific and

differentiation-dependent manner and mediate adhesion by forming strong extracellular homo/heterophilic bonds. At the intracellular level, their extremities interact with plakoglobin (Pg) and plakophilins (Pkps) (Bass-Zubek *et al*, 2009) thus forming the *outer dense plaque*. These molecules bind to components of the *inner dense plaque*, namely desmoplakin (Dp) plectin, envoplakin (EVP), and periplakin (PPL), whose function is to anchor KIFs and stabilize desmosomes (Vasioukhin *et al*, 2001). In addition to this structural role, components of desmosomal plaques are also important for cell signalling and interaction with regulatory molecules such as kinases and proteases. This finely regulated network of intrinsic and accessory molecules constitutes the desmosomal functional unit, or desmo-adhesome (Cirillo and Prime, 2009).

To date, almost 30 different diseases (**Table 1**) in which desmosomes are impaired have been identified. These can be categorized into infectious, autoimmune, and inherited. Additionally, recent evidence has shown that desmosomal molecules are often dysregulated in cancer.

Autoimmune disease of the desmosome

Pemphigus disease

Among the acquired desmosomal diseases, a predominant role is surely represented by *Pemphigus*, a family of autoimmune diseases characterized by circulating autoantibodies that target desmosomal components as well other epithelial antigens and impair keratinocytes adhesion with subsequent acantholysis. The anti-desmosomal antibodies detected in pemphigus patients are directed against Dsg1 and/or Dsg3 (Cirillo *et al*, 2007). These diseases are considered relatively rare with an overall incidence of 1–16 new cases per million people / year (Ruocco *et al*, 2013) and the age of onset is usually the fifth or sixth decade of life. Although the precise pathomechanisms of pemphigus have not yet been fully elucidated, recent studies have shown that desmosome disassembling involves not only the direct inhibition of desmosome formation caused by IgGs, but also desmosome remodelling. Additionally, several intracellular signaling pathways possibly triggered by nondesmosomal molecules. The signalling-related events include apoptosis as well as

modulation of Pg, p38MAPK, heat shock protein 27, cdk2, Src, RhoA, and others (Kitajima, 2014; Cirillo, 2016).

The main subtypes of Pemphigus are pemphigus vulgaris (PV), pemphigus foliaceus (PF), paraneoplastic pemphigus (PNP) and IgA pemphigus (IAP).

- PV is the most common subtype of pemphigus (~70 % of cases), found mainly in middle-aged and elderly patients, with a female predisposition. Familial cases are rare although a higher incidence was found in Ashkenazi Jewish and Japanese populations (Joly and Litrowski, 2011). Histologically, PV is characterized by an intra-epidermal cleft between the basal and spinous layers (suprabasal acantholysis), which manifests clinically as painful mucosal lesions and skin blister formation. Oral mucosal lesions appear early and associate with the presence of anti-Dsg3, but not anti-Dsg1, antibodies. Early diagnosis and treatment is associated with a better prognosis (Mignogna *et al*, 2010) and may prevent the spreading of the disease to skin tissues. The muco-cutaneous type of PV is characterized by skin blisters in addition to oral erosions and associates with an autoantibody switch to both anti-Dsg1 and anti-Dsg3 IgG (Amagai 2010). In addition, autoantibodies in PV can target Dsc1, Dsc2, and Dsc3 (Stahley and Kowalczyk, 2015).

- PF variants represents about 20-30% of pemphigus cases and is characterized by superficial epidermal blisters without mucosal involvement. The blistering results from autoantibodies directed against Dsg1, and is restricted to the granular layer of the epidermis. Further desmosomal targets such as Dsc1, Dsc2, Dsc3, Pg, Dsp, and Pkp3 have been described in the literature.

- PNP is a rare form of pemphigus that typically affects patients diagnosed with malignancies such as non-Hodgkin's lymphoma and chronic lymphocytic leukemia (Yong and Tey, 2013). This variant is the most severe among pemphigus subtypes, and shows a distinctive set of clinical features including a typically polymorphous skin rash, severe mucosal involvement, life-threatening bronchiolitis and unusual histopathological and immunological findings (Hata *et al*, 2013). The age of onset is usually 45–70 years, and intraorally, PNP is characterized by extremely painful and refractory lesions potentially followed by full body cutaneous involvement. Unlike other pemphigus subtypes, PNP can show the involvement of palms and/or soles, conjunctiva, and simple squamous epithelia.

The desmosome proteins targeted by autoantibodies in PNP are several, and include Dsgs (particularly the Dsg3), Dscs, Dsp and plakophilins (Stahley and Kowalczyk,

2015), as well as EVP, PPL, and a number of less well-specified antigens such as alpha-2-macroglobulin-like-1 (Schepens *et al*, 2010). Patients presenting with immunological profiles suggestive of PNP and without evidence of malignancy deserve strict follow-up for the possible subsequent development of cancer. The prognosis of PNP remains poor, with mortality rates reaching 90% (Yong and Tey, 2013).

- IAP is a subtype characterized by the presence of circulating IgA autoantibodies that can target desmosomal and non-desmosomal keratinocyte cell surface constituents. IAP in turn is divided into two subtypes: the subcorneal pustular dermatosis (s-c), in which Dsc1 is the target antigen, and the intra-epidermal neutrophilic dermatosis (i-e) in which the targets are Dsg1 and Dsg3. Recently, a comparative clinicopathologic study has established that IgG/IgA pemphigus, a further overlapping variant between classic IgG pemphigus and IAP, may best be regarded as a variant of IgG pemphigus and distinct from IgA pemphigus (Toosi *et al*, 2016). Histologically IAP is characterized by acantholysis and extensive neutrophilic infiltration within the upper layers or all layers of the epidermis. Reports of patients with IAP are sparse, with only about 60 cases described, though the prognosis of this form was rated as comparable with the classic forms of pemphigus.

Erythema multiforme (EM) and Stevens-Johnson syndrome (SJS)

Besides the pemphigus group, desmosomes have shown to be targeted in Erythema multiforme (EM) and Stevens-Johnson syndrome (SJS) cases. EM and SJS are two acute immune-mediated disorders that can affect the skin and mucous membranes through a type 4 cytotoxic reaction, mediated by T lymphocytes and triggered by numerous factors. Several reports described circulating autoantibodies to Dsp1 and Dsp2 in EM patients (Johnson *et al*, 1999; Ellis and Sidhu, 2014). So far, the pathogenic significance of the circulating Dsp autoantibodies in EM and SJS has not yet been elucidated. The unsolved question is whether there is a subset of EM patients with autoimmune disease or they are a manifestation of the phenomenon of epitope spreading.

Infectious diseases of the desmosome

Disruption of desmosome integrity can be caused by infective agents. *Bullous impetigo* (BI) and *Staphylococcal scalded skin syndrome* (SSSS) are caused by *Staphylococcus aureus* through the release of exfoliative toxin, a serine protease that specifically cleaves the extracellular domain of Dsg1 (Amagai *et al*, 2000). *Respiratory and urinary tract infections* caused by adenovirus serotypes (Ad) 3, 7, 11 and 14, can target Dsg2 (Amagai and Stanley, 2012). *Giardiasis* (Gd) targets Dsc2/3 and disrupts tight, adherens and desmosomal junctions of intestinal cells (Adam, 2001). Lastly Dsp and Pg of alveolar epithelial cells can be targeted by *Bacillus anthracis* lethal toxin (BA-LT), with a consequent impaired desmosome assembly (Langer *et al*, 2012). These infectious diseases have limited oral involvement and their discussion goes beyond the scope of this review. More details can be found in **table 1**. Desmosome disruption and anomalies have been also linked to coxsackievirus B3 (CVB3) and infections of the oral mucosa, although the specific targets remain unknown (Stahley and Kowalczyk, 2015).

Genetic diseases of the desmosome

Diseases resulting from genetic alterations of desmosomal components involve skin and hearth tissues but have limited oral involvement. Details are reported in **Table 1**.

Striated palmoplantar keratoderma (SPPK) and *Palmoplantar keratoderma* (PPK) feature mutations in the Dsg1, Pkp1 and Dsp genes (Cirillo, 2016). *Severe skin dermatitis, multiple allergies and metabolic wasting syndrome* (SAM) is linked to mutations in Dsg1 (Samuelov *et al*, 2013) and Dsp genes (McAleer *et al*, 2015). *Localized autosomal recessive hypotrichosis* (LAH) is caused by several mutations in the Dsg4 gene (Moss *et al*, 2004). *Recessive monilethrix* may also be linked to Dsg4 mutations. *Ectodermal dysplasia-skin fragility syndrome* (EDFSF) is caused by mutations in the Pkp1 gene, whereas *Lethal congenital epidermolysis bullosa* features homozygous nonsense mutation, that leads to the lack of Pg.

Desmosome-like structures are also present in cardiac muscle cells, and mutations of desmosomal components results in hearth disease. *Arrhythmogenic right ventricular*

dysplasia/cardiomyopathy (ARVD/C) and Left dominant arrhythmogenic cardiomyopathy involve several mutations in the Dsg2, Dsc2, Pg, Dsp2, and Pkp2 genes (Awad *et al*, 2006; Nagaoka *et al*, 2006; Syrris *et al*, 2006). Another variant of the disease named *lethal acantholytic epidermolysis bullosa* has also been identified as the result of heterozygosity of two loci containing the C terminus of Dsp and leading to the formation of a truncated protein, thus lacking the entire IF-binding domain. *Brugada syndrome* has been linked to 18 different gene mutations, one being *PKP2* (ENSG00000057294) which encodes for the protein plakophilin-2 (PKP2).

In certain cases, both epidermis and heart can be affected. *Woolly hair*, an autosomal recessive structural abnormality of scalp hair is a clinical feature shared syndromically with palmoplantar hyperkeratosis and heart anomalies by diseases targeting Dsc2, Pg (e.g. *Naxos disease*), and Dp (e.g. *Carvajal syndrome*).

Desmosome and cancer

David Garrod's group first proposed a mechanistic role of desmosomes in cancer progression (Tselepis *et al*, 1998). To date, at least three mechanisms through which alteration of desmosomal cadherins occurs in cancer have been identified, namely: (1) transcriptional regulation of desmosomal cadherins; (2) impaired transport, targeting, and assembly into mature desmosomes; and lastly, (3) inactivation by proteolytic cleavage. Furthermore, the control of cell cycle as well as apoptosis can be indirectly affected by desmosomal cadherin signalling function.

The idea that the loss of intercellular adhesion could be directly related to cancer invasiveness is fairly predictable. Surprisingly, analysis of the expression levels of desmosomal components in cancer have yielded conflicting results. Specifically, expression of desmosomal cadherins was found to be decreased in many tumours such as skin, head and neck, lung, breast, prostate, cervix etc., but reported as increased by others (Huber and Petersen, 2015).

There is however compelling clinical evidence that correlates desmosomal deregulation with clinic-pathologic features of the tumour including staging and grading, and consequently prognosis. This is the case of renal cell carcinoma, prostate cancer, endometrial carcinoma, head and neck cancer, lung cancer, gastric and colon

cancer, pancreatic ductal adenocarcinoma, SCC of the sinonasal cavity, cutaneous SCC, esophageal adenocarcinoma, and not least OSSC.

Thus, current evidence strongly suggests that desmosomal proteins will soon assume a main role as cancer markers/prognostic factors, but also as potential molecular targets for development of novel therapies.

We refer the reader to a couple of recent review articles for a comprehensive discussion of this topic (Stahley and Kowalczyk, 2015; Huber and Petersen, 2015).

Diagnostic Pathway

The aim of this section is to provide guidance to dentists and oral medicine specialists for the diagnosis of desmosome-related conditions, especially blistering diseases, and to outline the rationale for the diagnostic investigations required.

The diagnosis of blistering disease is reached from the combination of clinical, histological, immuno-pathological, and serological findings, the latter being a prerequisite for the diagnosis of immuno-bullous disorders. Genetic disease can be confirmed by gene mutation analysis. Additional tests may include immunoblotting, immunoprecipitation, and electron microscopy.

Clinical evaluation

Diseases of the pemphigus group dominate the field of desmosome-related conditions with oral manifestations, and hence are more relevant to dental practitioners. Clinical evaluation includes examination of the skin, mucous membranes and nails and patients should be also questioned for symptoms suggestive of on extraoral mucosal involvement. The patient's medical history and medications should be thoroughly reviewed, since clinical and laboratory studies may not discriminate between idiopathic and drug-induced pemphigus. Despite some clinical findings being suggestive of specific immunobullous diseases, e.g. flaccid blisters and a positive Nikolsky sign for PV, laboratory-based detection of tissue-binding and circulating autoantibodies is always required.

A standard laboratory work-up for these patients would include:

- A lesional skin/mucosal biopsy for routine hematoxylin and eosin (H&E) staining
- A perilesional skin/mucosal biopsy for direct immunofluorescence (DIF), and/or

- Serum collection for indirect immunofluorescence (IIF) and enzyme-linked immunosorbent assay (ELISA).

Sample collection

The biopsy for routine histopathology should ideally be performed on an intact lesion and a punch biopsy (4mm) is usually sufficient. Clinicians may prefer to employ a stab-and-roll technique using size 15 scalpel blade to maintain the epithelial roof in the sample. The sample should be placed immediately in 10% buffered formalin.

A tissue sample for DIF microscopy should be taken from the perilesional area to contain both epithelium and stroma. The sample should be placed this time in optimal cutting temperature (OCT) compound and frozen immediately at -20°C and stored at -80°C until processing. If OCT compound is not available, the tissue may alternatively be placed in normal saline-soaked gauze and kept at 4°C, or in Michel's medium that can preserve the sample at room temperature for approximately 6 months (Vodegel *et al*, 2004).

Biopsy for transmission electron microscopy (TEM) and immuno-mapping are identical to that for routine histopathology. The sample should be placed immediately in an electron-microscopy-specific medium, and in OCT respectively.

ELISA and IIF assays are used for serodiagnosis and require the collection of a 5-10 mL blood sample without anticoagulants. This is then centrifuged to separate plasma (which contains the gamma globulins) from blood cells.

Histology

The characteristic histopathological findings in PV include intraepithelial cleavage with loss of keratinocytes adhesion, known as acantholysis, localized primarily to the suprabasal region. Retention of basal keratinocytes along the basement membrane zone results in an appearance that resembles a "row of tombstones". There is additionally sparse inflammatory infiltrate in the dermis with eosinophils. In the variant known as pemphigus vegetans, the suprabasal cleavage is accompanied by hyperkeratosis, papillomatosis, and prominent acanthosis with downward proliferation of the rete ridges.

The characteristic histopathological findings of PF include intraepithelial acantholysis beneath the stratum corneum or within the granular layer, occasional presence of

neutrophils within the blister cavity and mixed inflammatory infiltrate in the superficial dermis with neutrophils and eosinophils.

Typical histopathological findings of IAP include intraepidermal clefts and pustules located in a subcorneal location (s-c) or in the entire or mid-epidermis (i-e), slight or absent acantholysis and a mixed inflammatory infiltrate in the dermis.

The most common histopathological findings in PNP are suprabasal acantholysis, keratinocyte necrosis, and a lichenoid interface dermatitis. However, in PNP the histopathologic findings are variable.

The histopathological features of all other desmosomal diseases with limited involvement of the oral cavity are reported in **Table I**.

Direct immunofluorescence microscopy (DIF)

DIF is a technique that aims to detect any in situ deposition of immunoreactants (typically immunoglobulins and/or complement components) in patients' epidermis or mucous membranes. Detection of the immune deposits in the sample allows confirmation of presumed immunological pathomechanism, and classification of the disease according to the exact location of the immune deposits. The most common antibodies used for DIF comprise fluorescein-conjugated antibodies against IgG, IgM, IgA, C3, and fibrinogen. IF microscopy is still considered the diagnostic gold standard for pemphigus given that the tissue fixed intercellular antibodies are present in about 90% of the patients. In both PV and PF, an intercellular binding of IgG and/or C3 is found in a typical “cobblestone” or “fish-net pattern” in the epidermis/epithelium while in PNP, in addition to the above findings, an abnormal band-like deposit of immunoglobulin/complement are detected in the dermal—epidermal junction (Chiorean *et al*, 2014). In IAP the main finding is the deposition of IgA with an intercellular pattern. Importantly, cryosections of perilesional biopsies are required for direct IF microscopy.

Indirect immunofluorescence microscopy (IIF)

IIF aims to detect circulating autoantibodies in patients' sera that target skin constituents. The procedure applies patient serum to normal epithelial substrate in a two incubation steps. One of the most used epithelial substrate is the monkey esophagus. In general, it is well established that the type of substrate used influences the sensitivity of the test. More in detail, for PV and PF the best substrates are

monkey and guinea pig esophagus, respectively. For PNP, rat or monkey bladder is used due to their high expression of plakins. Interestingly, more than 80% of PV and PF patients have detectable circulating autoantibodies (Payne and Stanley, 2012), which makes IIF a reliable technique for the diagnosis of these autoimmune blistering diseases.

In IAP the preferred substrate is monkey esophagus, and binding of autoreactive IgA from patient's sera to epithelial cells with an intercellular pattern may be found. Only recently a novel IF assay using desmocollin-transfected COS-7 cells is available to characterize autoreactive IgA molecular specificity (Otten *et al*, 2014).

The staining patterns are similar to those described for DIF.

ELISA

ELISA is a technique that measures specific autoantibodies in serum. Test serum is incubated in microtiter plate wells that are coated with the antigen(s) of interest. Matched autoantibodies will bind to the antigen and the incubation with an enzyme conjugated secondary anti-IgG antibody, resulting in proportional colour change. In PV and PF, serum levels of anti-Dsg1 and anti-Dsg3 antibodies may be related to disease activity (Cirillo *et al*, 2012). This test can also be useful to assess response to treatment (Zone, 2009). In general, anti-Dsg1 levels better correlate to disease course in PV and PF patients than anti-Dsg3 levels, which may remain high even in phases of remission (Abasq *et al*, 2009). ELISA kits are commercially available for detection of serum IgG antibodies to Dsg1/Dsg3. ELISA assay, with a sensitivity that exceeds 90 percent, has been demonstrated to be more sensitive and specific than IIF for the diagnosis of PV and PF (Payne and Stanley, 2012).

In general, the following outcomes may be expected:

- in PV with exclusive mucosal involvement, anti-Dsg3 will be detected whereas in mucocutaneous variant both Dsg1 and Dsg3 autoantibodies can be found.
- PF is characterized by exclusive involvement of Dsg1 autoantibodies.
- In most cases of PNP IgG autoantibodies against Dsg1 and Dsg3 are found but also against Dsc1/Dsc3/EVP/PPL, followed by Dsp1/Dsp2/plectin, and BP230.

- IgA pemphigus is characterized by the detection of IgA autoantibodies against Dsg1 and Dsg3 in the i-e type and against Dsc1 in the s-c type. (Kneisel and Hertl 2011).

The ELISA system for detection of anti-envoplakin antibodies is now commercially available. Conversely, ELISA for detection of other molecules such as desmocollins, periplakin, whilst already available, have not yet been released for routine clinical diagnostic use.

Additional test: immunoblotting and immunoprecipitation, protein arrays, PCR, gene sequencing

Togheter with ELISA, immunoblotting (also referred to as Western Blotting) and immunoprecipitation are highly sensitive and specific detection techniques of autoantibodies that use recombinant autoantigens or keratinocyte extracts from healthy human skin. Recently, protein microarrays has proven to be a powerful technique to detect large number of autoantibodies in blistering disease (Kalantari-Dehaghi et al., 2013).

Immunoprecipitation is more sensitive than immunoblotting and in particular is used for immunoserological follow-up and as definitive serological confirmatory test. Remains, however, to consider that Western blotting analysis is not necessarily useful in pemphigus diagnosis given that most of the immunogenic epitopes on Dsg1 and 3, are conformational. The increasing complexity of autoantibody profiles in blistering diseases will probably be addressed by protein arrays in future years.

Together with clinical and histological findings, the diversity and heterogeneity of some genetic desmosomal diseases make genetic testing indispensable for diagnosis, assuming that the causative genes have been identified. In general, single base pair mutations are identified by direct sequencing, DNA hybridization and/or restriction enzyme digestion methods.

Concluding remarks

Alteration of desmosomal components leads to diseases that feature skin, cardiac and oral involvement. The desmosome offers a precious example of how basic,

translational, and clinical research integrate and support each other to gain insight into the understanding of human diseases and, ultimately, to improve patient management.

References

1. Abasq C, Mouquet H, Gilbert D, Tron F, Grassi V, Musette P, Joly P (2009). ELISA testing of anti-desmoglein 1 and 3 antibodies in the management of pemphigus. *Arch Dermatol* **145**: 529-35.
2. Adam RD (2001). Biology of Giardia lamblia. *Clin Microbiol Rev* **14**: 447–475.
3. Amagai M, Matsuyoshi N, Wang ZH, Andl C, Stanley JR (2000). Toxin in bullous impetigo and staphylococcal scalded-skin syndrome targets desmoglein 1. *Nat Med* **6**: 1275-7.
4. Amagai M (2010). Autoimmune and infectious skin diseases that target desmogleins. *Proc Jpn Acad Ser B Phys Biol Sci* **86**: 524–537.
5. Amagai M, Stanley JR (2012). Desmoglein as a target in skin disease and beyond. *J Invest Dermatol* **132**: 776-84.
6. Awad MM, Dalal D, Cho E, Amat-Alarcon N, James C, Tichnell C, Tucker A, Russell SD, Bluemke DA, Dietz HC, Calkins H, Judge DP (2006). DSG2 mutations contribute to arrhythmogenic right ventricular dysplasia/cardiomyopathy. *Am J Hum Genet* **79**: 136-42.

- 455
- 456 7. Bass-Zubek AE, Godsel LM, Delmar M, Green KJ (2009). Plakophilins:
457 multifunctional scaffolds for adhesion and signaling. *Curr Opin Cell Biol* **21**:
458 708-716.
- 459
- 460 8. Bizzozzero G (1864). Delle cellule cigliate, del reticolo Malpighiano
461 dell'epidermide. *Ann Univ Med* **190**: 110–118.
- 462
- 463 9. Chiorean R, Mahler M, Sitaru C (2014). Molecular diagnosis of autoimmune
464 skin diseases. *Rom J Morphol Embryol* **55**(3 Suppl): 1019-33.
- 465
- 466 10. Cirillo N (2016). Desmosome assembly, homeostasis, and desmosomal
467 disease. *Cell Health and Cytoskeleton* **8**: 9-23.
- 468
- 469 11. Cirillo N, Gombos F, Lanza A (2007). Pemphigus vulgaris immunoglobulin G
470 can recognize a 130 000 MW antigen other than desmoglein 3 on peripheral
471 blood mononuclear cell surface. *Immunology* **121**: 377-82.
- 472
- 473 12. Cirillo N, Prime SS (2009). Desmosomal interactome in keratinocytes: a
474 systems biology approach leading to an understanding of the pathogenesis of
475 skin disease. *Cell Mol Life Sci* **66**: 3517-33.
- 476
- 477 13. Cirillo N, Cozzani E, Carrozzo M, Grando SA (2012). Urban legends:
478 pemphigus vulgaris. *Oral Dis* **18**: 442-58.
- 479
- 480 14. Ellis E, Sidhu S (2014). Circulating plakin autoantibodies in a patient with
481 erythema multiforme major: are they pathogenic or a manifestation of epitope
482 spreading? *Australas J Dermatol* **55**: 266-9.
- 483
- 484 15. Hata T, Nishimoto S, Nagao K, Takahashi H, Yoshida K, Ohyama M,
485 Yamada T, Asano K, Amagai M (2013). Ectopic expression of epidermal
486 antigens renders the lung a target organ in paraneoplastic pemphigus. *J*
487 *Immunol.* **191**: 83-90.
- 488

16. Huber O, Petersen I (2015). 150th Anniversary Series: Desmosomes and the Hallmarks of Cancer. *Cell Commun Adhes* **22**: 15-28.
17. Johnson SM, Smoller BR, Horn TD (1999). Erythema multiforme associated with human autoantibodies against desmoplakin I and II. *J Invest Dermatol* **112**: 395-6.
18. Joly P, Litrowski N (2011). Pemphigus group (vulgaris, vegetans, foliaceus, herpetiformis, brasiliensis). *Clin Dermatol* **29**: 432-6.
19. Kalantari-Dehaghi M, Anhalt GJ, Camilleri MJ, Chernyavsky AI, Chun S, Felgner PL, Jasinskas A, Leiferman KM, Liang L, Marchenko S, Nakajima-Sasaki R, Pittelkow MR, Zone JJ, Grando SA (2013) Pemphigus vulgaris autoantibody profiling by proteomic technique. *PLoS One* **8**: e57587.
20. Kitajima Y (2014). 150(th) anniversary series: Desmosomes and autoimmune disease, perspective of dynamic desmosome remodeling and its impairments in pemphigus. *Cell Commun Adhes* **21**: 269-80.
21. Kneisel A, Hertl M (2011). Autoimmune bullous skin diseases. Part 2: diagnosis and therapy. *J Dtsch Dermatol Ges* **9**: 927-47.
22. Langer M, Duggan ES, Booth JL, Patel VI, Zander RA, Silasi-Mansat R, Ramani V, Veres TZ, Prenzler F, Sewald K, Williams DM, Coggeshall KM, Awasthi S, Lupu F, Burian D, Ballard JD, Braun A, Metcalf JP (2012). *Bacillus anthracis* lethal toxin reduces human alveolar epithelial barrier function. *Infect Immun* **80**: 4374-87.
23. McAleer MA, Pohler E, Smith FJ, Wilson NJ, Cole C, MacGowan S, Koetsier JL, Godsel LM, Harmon RM, Gruber R, Crumrine D, Elias PM, McDermott M, Butler K, Broderick A, Sarig O, Sprecher E, Green KJ, McLean WH, Irvine AD (2015). Severe dermatitis, multiple allergies, and metabolic wasting syndrome caused by a novel mutation in the N-terminal plakin domain of desmoplakin. *J Allergy Clin Immunol* **136**: 1268-76.

24. Mignogna MD, Fortuna G, Leuci S, Ruoppo E (2010). Oropharyngeal pemphigus vulgaris and clinical remission: a long-term, longitudinal study. *Am J Clin Dermatol* **11**: 137-45.
25. Moss C, Martinez-Mir A, Lam H, Tadin-Strapps M, Kljuic A, Christiano AM (2004). A recurrent intragenic deletion in the desmoglein 4 gene underlies localized autosomal recessive hypotrichosis. *J Invest Dermatol* **123**: 607-10.
26. Nagaoka I, Matsui K, Ueyama T, Kanemoto M, Wu J, Shimizu A, Matsuzaki M, Horie M (2006). Novel mutation of plakophilin-2 associated with arrhythmogenic right ventricular cardiomyopathy. *Circ J* **70**: 933-5.
27. Otten JV, Hashimoto T, Hertl M, Payne AS, Sitaru C (2014). Molecular diagnosis in autoimmune skin blistering conditions. *Curr Mol Med* **14**: 69-95.
28. Payne AS, Stanley JR (2012). Pemphigus. In: Fitzpatrick's Dermatology in General Medicine. 8th edition. Goldsmith LA, Katz SI, Gilchrest BA, et al. (Eds), McGraw Hill, Vol 1, p.586.
29. Ruocco V, Ruocco E, Lo Schiavo A, Brunetti G, Guerrera LP, Wolf R (2013). Pemphigus: etiology, pathogenesis, and inducing or triggering factors: facts and controversies. *Clin Dermatol* **31**: 374-81.
30. Samuelov L, Sarig O, Harmon RM, Rapaport D, Ishida-Yamamoto A, Isakov O, Koetsier JL, Gat A, Goldberg I, Bergman R, Spiegel R, Eytan O, Geller S, Peleg S, Shomron N, Goh CS, Wilson NJ, Smith FJ, Pohler E, Simpson MA, McLean WH, Irvine AD, Horowitz M, McGrath JA, Green KJ, Sprecher E (2013). Desmoglein 1 deficiency results in severe dermatitis, multiple allergies and metabolic wasting. *Nat Genet* **45**: 1244-1248.
31. Schepens I, Jaunin F, Begre N, Läderach U, Marcus K, Hashimoto T, Favre B, Borradori L (2010). The protease inhibitor alpha-2-macroglobulin-like-1 is the

- p170 antigen recognized by paraneoplastic pemphigus autoantibodies in human. *PLoS One* **5**: e12250.
32. Stahley SN, Kowalczyk AP (2015). Desmosomes in acquired disease. *Cell Tissue Res* **360**: 439-56.
33. Syrris P, Ward D, Asimaki A, Sen-Chowdhry S, Ebrahim HY, Evans A, Hitomi N, Norman M, Pantazis A, Shaw AL, Elliott PM, McKenna WJ (2006). Clinical expression of plakophilin-2 mutations in familial arrhythmogenic right ventricular cardiomyopathy. *Circulation* **113**: 356-64.
34. Toosi S, Collins JW, Lohse CM, Wolz MM, Wieland CN, Camilleri MJ, Bruce AJ, McEvoy MT, Lehman JS (2016). Clinicopathologic features of IgG/IgA pemphigus in comparison with classic (IgG) and IgA pemphigus. *Int J Dermatol* **55**: e184-90.
35. Tselepis C, Chidgey M, North A, Garrod D (1998). Desmosomal adhesion inhibits invasive behavior. *Proc Natl Acad Sci U S A* **95**: 8064-9.
36. Vasioukhin V, Bowers E, Bauer C, Degenstein L, Fuchs E (2001). Desmoplakin is essential in epidermal sheet formation. *Nat Cell Biol* **3**: 1076-1085.
37. Vodegel RM, de Jong MC, Meijer HJ, Weytingh MB, Pas HH, Jonkman MF (2004). Enhanced diagnostic immunofluorescence using biopsies transported in saline. *BMC Dermatol* **4**:10.
38. Wang Q, Peng D, Zhu S, Chen Z, Hu T, Soutto M, Saad R, Zhang S, Ei-Rifai W (2014). Regulation of Desmocollin3 Expression by Promoter Hypermethylation is Associated with Advanced Esophageal Adenocarcinomas. *J Cancer* **5**: 457-64.
39. Yong AA, Tey HL (2013). Paraneoplastic pemphigus. *Australas J Dermatol* **54**: 241-50.

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40. Zone JJ (2009). The value of desmoglein 1 and 3 antibody ELISA testing in patients with pemphigus. *Arch Dermatol* **145**: 585-7.

	DISEASE	MOLECULAR TARGET(S)	MANIFESTATIONS		HISTOLOGY	IMMUNOFLUORESCENCE	ADDITIONAL DIAGNOSTIC TOOLS
			INTRAORAL	EXTRAORAL			
AUTOIMMUNE	PV	Dsg1, Dsg3, Dsc1, Dsc2, Dsc3	Painful refractory erosions and ulcers of the oral mucosa	Flaccid bullae and erosions on skin. Lesions of: lips, pharynx, larynx, esophagus, eyelid conjunctiva and vagina.	Suprabasal acantholysis; "row of tombstones" pattern of basal keratinocytes; sparse inflammatory infiltrate in the dermis with eosinophils	DIF: Intraepidermal intercellular deposition of IgG and/or C3, in a "cobblestone" or "fishnet" pattern IIF: Intercellular deposition of IgG; (monkey esophagus is preferred substrate)	ELISA: Dsg1 and Dsg3 autoantibodies Protein microarrays: additional non-Dsg IgGs
	PF	Dsg1, Dsc1, Dsc2, EVP, PPL	Mucosal involvement absent	Fragile blisters, shallow erosions, erythematous patches, crusts most frequently affecting head, face, chest and back	Subcorneal or granular layer acantholysis; mixed inflammatory infiltrate in the superficial dermis with eosinophils and neutrophils	DIF: Intercellular deposition of IgG IIF: Intercellular deposition of IgG; (normal human skin or monkey esophagus)	ELISA: Dsg1 autoantibodies
	PNP	Dsg1, Dsg3, Dsc2, Dsc3, Pg, Pkp1, Pkp2, Pkp3, Dsp1, Dsp2, EVP, PPL, Plectin, epiplakin, BP230, A2ML1	Severe and extensive mucosal erosions and ulcerations crusting of vermillion border	variable cutaneous findings, eg: blisters, erosions, lichenoid lesions, bronchiolitis obliterans; severe mucous membrane involvement	Variable findings: suprabasal acantholysis, keratinocyte necrosis, and lichenoid interface dermatitis are most common	DIF: Intercellular and/or basement membrane zone deposition of IgG and/or C3 IIF: Intercellular deposition of IgG (rat bladder is preferred substrate)	ELISA: IgG autoantibodies to Dsg1, Dsg3, Dsc1, Dsc3, EVP, PPL, Dsp1, Dsp2, plectin, and BP230
	IAP (i-e)	Dsg1, Dsg3, Dsc1	Mucosal involvement usually absent	Vesicles, pustules, crusts on skin; annular, circinate, or herpetiform morphology	Intraepidermal pustules; minimal acantholysis; mixed infiltrate in dermis	DIF: Intercellular deposition of IgA* IIF: Intercellular deposits of IgA* (on monkey esophagus)	ELISA: Dsg1 and Dsg3 autoantibodies have been reported in some patients
	IAP (s-c)	Dsc1	Subcorneal clefts and pustules; minimal acantholysis; mixed infiltrate in dermis		ELISA: Dsc1 autoantibodies¶		
	EM/ SJS	Dsp	Variable: erosive/bullous lesions. The buccal mucosa, vermillion border, and labial mucosa are the most commonly affected sites	Variable mucocutaneous involvement: isolated symmetric targetoid lesions commonly distributed on the extensor surfaces of the Extremities, hands, elbows and knees with extensive involvement of the arms, legs, and trunk. can affect >10% of BSA	Variable: usually non-specific inflammatory infiltration with rare eosinophils with/without subepidermal blistering; confluent keratinocyte apoptosis and focal basal vacuolar degeneration, necrosis, intraepithelial exocytosis, Civatte bodies, edematous corium	DIF: Strongly positive linear staining for C3 and weakly positive immunoglobulin G IIF: Can be positive	ELISA: Peptide-specific Dp Autoantibodies (PMID: 16086758) PCR: to assess HSV and M. Pneumoniae presence.
INFECTIOUS	BI	Dsg1	Flaking and fissuring of the lips	Small vesicles that evolve in large flaccid bullae usually affecting the trunk, perineum, periumbilical area and the extremities. Lesions rupture and leave a thin brown crust.	Intraepidermal cleavage, beneath or within the granular layers; the blister cavities become filled with neutrophils and the underlying dermis contains mixed infiltrates of neutrophils and lymphocytes	Not usually indicated	ELISA: No apparent IgM reactivity against Dsg1 or Dsg3 Gram stain and culture: of pus or exudate is recommended to identify whether S. aureus and/or a beta-hemolytic Streptococcus is the cause
	SSSS	Dsg1	Lack of mucous membrane involvement; Perioral manifestation: Flaking and fissuring of the lips	Diffuse erythema, fever, positive Nikolsky's sign. Rash that evolves in lesions ranging from localized blisters to severe exfoliation of >90% of BSA	Subcorneal cleavage, Presence of only a stratum corneum with a single epidermal cell layer; absence of necrotic keratinocytes.	Not usually indicated	ELISA: low titers of anti-Dsg1 IgG autoantibodies Gram stain and culture: swab of the skin, orificial areas, and mucous membranes for bacterial identification and screening for Staphylococcus aureus carriage.
	Respiratory and urinary tract infections (ad 3,7,11 & 14),	Dsg2	Exudative tonsillitis	Pharyngitis and coryza, acute respiratory disease, bronchitis, pneumonia, pharyngoconjunctival fever, conjunctivitis, laryngotracheitis, fever, malaise, headache, myalgia, abdominal pain, otitis media, acute hemorrhagic cystitis, meningitis, myocarditis, myositis	Not usually indicated	Not usually indicated	ELISA: adenovirus-specific ELISA kit is commercially available. Viral culture: of the nasopharynx or throat PCR and real-time PCR adenovirus detection
	GD	Dsc2, Dsc3	50% of patients clear the infection in absence of clinical symptoms <u>Acute giardiasis</u> diarrhea (90%), malaise (86%), foul-smelling and fatty stools (steatorrhea) (75%), abdominal cramps and bloating (71%), flatulence (75%), nausea (69%), weight loss (66%), vomiting (23%), fever (15%) constipation (13%), urticaria (10%) <u>Chronic giardiasis</u> loose stools but usually not diarrhea, steatorrhea, profound weight loss (10 to 20 % of body weight), malabsorption,	Histopathological exam require a lot of effort and experienced staff . lead to false results in 10-50% of the cases. Diagnosis is made with direct observation of the cysts or trophozoites microscopically in the stool or duodenal fluid or examination of small intestinal samples and biopsies.	DIF: fluorescent monoclonal antibodies binding specifically to G. intestinalis cysts are used (sensitivity 100%, specificity 100%)	ELISA: Monoclonal ELISA detect G. intestinalis cyst antigens in the stool (sensitivity 88-99%, specificity 100%). Various nucleic acid amplification techniques: (NAATs), MICROSPHERES (Luminex), or LAMP (loop-mediated isothermal amplification) isothermal amplification of DNA are available	

			malaise, fatigue, depression, abdominal cramping, borborygmi, flatulence, burping				
	BA-LT (Anthrax)	Pg, Dsp	Oropharyngeal: Pseudo-membranous ulcers and necrosis reported to be localized at base and dorsal surface of the tongue, hard palate, soft palate, uvula, and tonsils	Fever, malaise, lymphadenopathy and headache. Cutaneous: small, painless, often pruritic papule with central vesicle or bulla, followed by erosion, painless necrotic ulcer with a black, depressed eschar. Extensive edema of surrounding tissues usually present Gastrointestinal: Ulcerations can occur in the stomach, esophagus, and duodenum and may result in gastrointestinal hemorrhage Respiratory: hemorrhagic necrosis of the thoracic lymph nodes draining the lungs, that can result in a hemorrhagic mediastinitis and necrotizing pneumonia	Bacilli presence easily identifiable. Focal hemorrhage, necrosis, edema, and congestion. Infiltration by neutrophils and prominent immunoblasts, various degrees of mononuclear inflammation, cyst formation	DIF: intracellular distribution and fine structure of ZO-1, E-cadherin, and β -catenin are altered by lethal toxin in alveolar epithelial cells	ELISA: detection of anti-protective antigen (PA) immunoglobulin (Ig)G Standard culture and Susceptibility testing IHC: The organism can be identified by direct observation through immunohistochemical staining. PCR: LRN, Standard or RT polymerase chain reaction can be performed on a variety of specimen types, including blood cultures, tissue samples, and blood samples.
GENETIC	PPK	Dsc2, Pkp1	perioral hyperkeratotic plaques with severe pruritus, hypodontia and dental defects, periodontitis, leukokeratoses and leukoplakia can be present	Thick, mild, or severe diffuse hyperkeratosis, hyperhidrosis	Epidermolytic or non-epidermolytic hyperkeratosis. Enlarged intercellular spaces and partial separation of keratinocytes	Not indicated	Genetic test: responsible gene: Dsg1, KRT1, KRT6c, KRT9, KRT16, SERPINB7, AQP5, SLURP1, TRPV3, AAGAB, COOL14A1
	SPPK	Dsg1, Dsp		Keratinization of sites exposed to trauma (knees ankles, knuckles etc.), mild nail dystrophy. Skin thickening is prominent in a linear pattern along the flexor aspects of the fingers and over pressure points on the soles.	Reduction in the number of desmosomes, accompanied by widening of intercellular spaces between suprabasal keratinocytes, and retracted KIFs	Not indicated	Genetic test: responsible gene: Dsg1 (MIM no. 148700), Dsp (MIM no. 612908), and KRT1 (MIM no. 607654)
	SAM	Dsg1	Limited oral involvement	Recurrent infections, severe metabolic wasting, severe PPK, severe erythroderma, severe dermatitis, skin erosion and scaling, multiple allergies, Elevated IgE, hard and curly hair, microcephaly, cardiac defects and hypotrichosis	psoriasiform dermatitis, with focal intracellular and intercellular edema and acantholysis within the spinous and granular layers	Not indicated	Genetic test: two homozygous mutations in Dsg1 gene
		Dsp	Marked hypodontia, poor periodontal health	Recurrent infections, Erythroderma, ichthyosis, PPK, nail dystrophy, diffuse hypotrichosis macrocephaly, a widespread superficial pustulosis, development delay and nystagmus, multiple food allergies, atopya, persistent eosinophilia, increased IgE levels	Irregular psoriasiform hyperplasia, hyperkeratosis and parakeratosis, and a mild superficial dermal inflammatory infiltrate, florid subcorneal pustular dermatosis		
	ARVD/C	Dsg2, Dsc2, Pkp2, Pkp4, Dsp	Oral involvement usually absent	myocardial atrophy and fibrofatty replacement of cardiac myocytes, ventricular arrhythmias, sudden cardiac death, syncope and end-stage heart failure, typically affecting the right ventricle	Endomyocardial biopsy (EMB) is not recommended	Not indicated	- Genetic test: truncating mutations in Dsp - ECG - Echocardiogram - Cardiac magnetic resonance
	Left dominant arrhythmogenic cardiomyopathy	Dsp	Oral involvement usually absent	palpitations, less frequent syncope, chest pain, dyspnea, and, rarely, sudden cardiac death	Endomyocardial biopsy (EMB) is not recommended	Not indicated	- Genetic test: truncating mutations in Dsp - ECG - Echocardiogram - Cardiac magnetic resonance
	LAH	Dsg4	Oral involvement usually absent	Hypotrichosis of the scalp, chest, arms and legs	Histology of scalp skin revealed thin and atrophic Hair Follicles and hair shafts that often coil up within the skin	Not indicated	- Genetic test: several mutations in the Dsg4 gene (18q12.1; 3q27.3; 13q14.11;13q21.32)

	Recessive monilethrix	Dsg4	Oral involvement usually absent	Moniliform hairs, pili torti, trichoschisis, trichorrhexis nodosa-like defects, tapered hairs	The presence of curled ingrown	Not indicated	- Genetic test: mutations in three type II hair cortex keratins (KRT8 ₁ ,KRT8 ₃ , KRT8 ₆), but may also be linked to Dsg4 mutations
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Curled ingrown hair shafts within the hair follicle

Wooly hair	Dsc2	Oral involvement usually absent	Hair with: elliptical cross section, variations in calibre, axis rotation, kinked formation, and non-homogeneous keratinization	Scalp biopsy is usually not necessary. An ophthalmologic examination is recommended for all patients with wooly hair. If a syndrome is suspected, an accurate cardiological exam is mandatory	Not indicated	- Genetic test: can be carried out when the gene locus is known - Hair examination: is carried out by light and electron microscopy - Trichogram
Naxos disease	Pg, Dsp	Leukokeratoses, and hypo/ oligodontia can be present	Familial wooly hair, diffuse non-epidermolytic PPK, ARVC with heart-rhythm disruptions	Not usually indicated	Not indicated	- Genetic test: can be carried out when the gene locus is known: Pg genetic defect located on chromosome 17q21; Dsp genetic defect located on chromosome 6p23-24
Carvajal syndrome	Dsp	hypo/oligodontia can be present	Dilated left ventricular Cardiomyopathy, wooly hair, keratoderma	Not usually indicated	Not indicated	- Genetic test: utosomal-dominant mutations in the DSP gene
EDFSF	Pkp1	perioral fissuring	Widespread skin fragility, non-cicatricial alopecia, PPK, nail dystrophy, hypohidrosis	Orthokeratosis, hypergranulosis and wide intercellular spaces between keratinocytes,	Not indicated	- Genetic test : At least eleven different recessively inherited mutations in the Pkp1 gene (chromosome 1q32) - Electron Microscopy: small poorly formed desmosomes and clumping of tonofilaments
Lethal congenital epidermolysis bullosa	Pg	Tongue mobility reduction	severe skin fragility, generalized epidermolysis, massive transcutaneous fluid loss, Oesophageal stenosis, Pyloric atresia	Pronounced acantholysis, and cleavage within the epidermis, with the loss of upper spinous, granular and horny layers. Basal keratinocytes were attached to the basement membrane but had only little or no contact to neighbouring and to suprabasal cells	DIF: abnormal expression and distribution of desmosomal and adherens junction protein. abnormalities of the dermal-epidermal basement membrane. (keratin 5 and 14, positive). Loss of cell-cell contacts in the basal layer. Loss of immunoreactivity to Dsp and Dsg3.	- Genetic test: homozygous nonsense JUP mutation, c.1615C>T, p.Q539X, that leads to the lack of Pg. - Electron Microscopy: structurally normal basement membrane and hemidesmosomes but loss of cell-cell contacts. Desmosomes were almost completely absent in the patient's skin; only very few desmosomal remnants could be observed
Lethal acantholytic epidermolysis bullosa	Dsp	Possible neonatal teeth	Complete alopecia, nail loss, cardiomyopathy, ears malformation, extensive neonatal epithelial shedding (>50% BSA), syndactyly, neonatal death	Acantholytic cell-poor intraepidermal blister with a single row of preserved but partially necrotic basal cells on the blister floor	DIF: on fresh frozen skin samples with anti-DP C-terminal antibodies provide a sensitive and quick screening method for DP C-terminal truncating mutations	- Genetic test: genomicDNA (gDNA) can be extracted from peripheral blood leucocytes, or from formalin-fixed paraffin-embedded (FFPE) skin tissue - Electron Microscopy: acantholysis in the entire epidermis. keratinocytes incompletely separated and swollen mitochondria indicating cell distress. Desmosomes reduced in number and very hypoplastic, inner dense plaque completely absent. mid cytoplasmic retraction of the tonofilament skeleton. Mean reduction of outer dense plaque diameter of the desmosomes. Hemidesmosomes appear slightly smaller and with reduced tonofilament insertion
Brugada syndrome	Pkp2	Absence of oral involvement	Life-threatening ventricular arrhythmias, Sudden cardiac arrest, atrial fibrillation, syncope, Nocturnal agonal respiration	From autopsy: Absence of active myocardial inflammation, moderate myocardial hypertrophy, moderate fibrosis and fatty replacement of the	Not indicated	- Genetic test: sequencing SCN5A gene commercially available Case by case evaluation of: - drug challenge (e.g. sodium channel

					myocardium (predominantly in the septum)		blockers), - signal-average ECG - invasive electrophysiology testing
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Legend:

*= Indirect immunofluorescence is negative in around 50 percent of patients with IgA pemphigus.

¶= Test availability restricted to specialized laboratories.

AC, Adenocarcinoma; **ARVD/C**, Arrhythmogenic right ventricular dysplasia/cardiomyopathy; **BA-LT** lethal toxin of *Bacillus anthracis*; **BSA**, Body surface area; **ECG**: electrocardiography; **EDSFS**, Ectodermal dysplasia-Skin fragility syndrome; **EM**, erythema multiforme; **Gd**, Giardiasis; **IAP (i-e)**, IgA pemphigus (intra-epidermal neutrophilic dermatosis); **IAP (s-c)**, IgA pemphigus (subcorneal pustular dermatosis); **LAH**, Localized autosomal recessive hypotrichosis; **MC**, Mucocutaneous type; **MD**, Mucosal dominant type; **PF**, Pemphigus foliaceus; **PG**, Plakoglobin; **PNP**, paraneoplastic pemphigus; **PPK**, palmoplantar keratoderma; **PV**, pemphigus vulgaris; **SAM**, Skin dermatitis multiple allergies and metabolic wasting syndrome; **SCC**, squamous cell carcinoma; **SJS**, Stevens-Johnson syndrome; **SPPK**, striate palmoplantar keratoderma; **SSSS**, staphylococcal scalded skin syndrome;

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