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Malignancy in Relation to Autoimmune Blistering Dermatoses: Molecular and Clinical Aspects

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1. Introduction

Autoimmune blistering dermatoses (ABD) are a group of relatively rare autoantibody-driven diseases affecting primarily skin and/or multiple mucosa. They comprise of two main subdivisions: ABD with autoimmunity to enzymes (dermatitis herpetiformis only) and ABD with autoimmunity to mostly structural proteins (anti-desmosomal autoimmunity circle, anti-dermal-epidermal junction autoimmunity circle and others). As both coexistent development of organ specific autoimmunity (e.g. myasthenia gravis) and transition between ABD groups are possible, ABD seem to be a part of pathological multiorgan autoimmunization syndrome [1]. The replacement of physiological autoimmunity by pathological autoimmunity and triggering blister formation in ABD still remain unexplored and essential issues. It is suggested that malignancy may be a triggering factor inducing the development of pathological autoimmunity. On the other hand, the development of malignancies during chronic immunosuppressive therapy may be observed [2].

In this chapter, we discuss an important and interesting area of research, focused on identifying the relationships, on both clinical and molecular level, between ABD and malignancy. Collectively, the literature data and our own experience indicate that ABD may be associated with different malignant tumors, both cutaneous and affecting internal organs. However, the issue if it is a mere coincidence or true pathogenetic relationship remains to be resolved. It is known that in a state of perpetual activation of immune system, as in ABD, proinflammatory molecules (e.g. cytokines) may cause tissue damage leading to chronic inflammation and subsequently increase the risk of carcinogenesis [3]. At both

clinical and molecular level ABD and malignancy-associated ABD (MAABD) may seem similar; nevertheless, the pathogenesis of those entities plausibly is fundamentally distinct. However, broadly observed associations between ABD and cancer indicate that various molecular pathways may contribute to elevated risk of malignancy in these patients. Most importantly, the coexistence of malignancy with ABD changes the management of such patients compared to patients with ABD alone. For a long months and years, many cases of ABD and MAABD are undiagnosed, misdiagnosed and subsequently mistreated due to relative rarity and therefore low awareness of autoimmunity-driven blistering dermatoses among practitioners. The time period elapsed between the first symptoms and diagnosis, makes the time-onset relation between ABD and cancer usually uncertain.

Molecular abnormalities of desmosomal proteins are observed in ABD and epithelial malignancies. A key function of desmosomal proteins is the maintenance of adhesion. However, in malignancy, where cells may separate, detach and metastasize, it is possible that alterations in their expression may be the reason of carcinogenesis process. Interestingly, the altered desmosomal protein expression and subsequent changes in cell-cell cohesion are often associated with signal pathways (e.g. epidermal growth factor – EGF in squamous cell carcinoma).

2. Autoimmune blistering dermatoses

ABD form a group of autoimmunity-driven diseases, where bullous lesions arise on the skin and/or multiple mucosa. Diverse ABD are evoked by different triggering mechanism and are characterized by different clinical onset, course and prognosis. Two main subdivisions can be separated: ABD with autoimmunity to enzymes and ABD with autoimmunity to structural proteins. The entities may be commonly distinguished by clinical, histopathological (presence or absence of acantholysis and differences of its localization, level of blistering and the composition of inflammatory infiltrate), immunohistochemical (localization and patterns of deposits and autoantibody immunoglobulin class) and molecular examination (ELISA, immunoblotting).

2.1. ABD with autoimmunity to enzymes

The entity is represented only by dermatitis herpetiformis (DH), also known as Duhring's disease - chronic, intensely itchy, blistering skin manifestation of the gluten sensitive enteropathy [4]. It affects symmetrically extensor surfaces of limps and the trunk – mainly buttocks and sacral area, where tiny vesicles, papules or even urticarial plaques occur in groups. The onset age is 20-60 years with peak about 35, and incidence ranging from 10 to 39 per 100,000 persons, depending on world region [1,5]. Patients have IgA autoantibodies to transglutaminases (TGs), that are considered major autoantigens in DH, yet other antigens were also reported (antiendomysial, antireticulin, antithyroid and antinuclear antibodies) [5]. It is thought that granular/fibrillar IgA deposits in tips of dermal papillae provoke neutrophile-mediated destruction of the dermal-epidermal junction (DEJ)

and forming subepidermal vesicle [1,4,5] Histopathologically, microabscesses in dermal papillae with neutrophile infiltration are seen in bioptate, obtained preferably of perilesional skin of the affected buttocks [5,6].

2.2. ABD with autoimmunity to structural proteins

This large group consists of several distinct circles of diseases with autoimmunity to different antigens – desmosomal, hemidesmosomal and others.

2.2.1. Anti-desmosomal autoimmunity circle / pemphigus group

Anti-desmosomal autoimmunity circle or pemphigus group refers to a group of chronic ABD characterized by the presence of autoantibodies (IgG or/and IgA) binding desmosomal structures and keratinocyte cell-surface antigens, leading to acantholysis and intraepithelial blister formation. The main antigens for pemphigus circle are desmoglein 1 (DSG1) and desmoglein 3 (DSG3), yet there are forms of pemphigus without anti-desmoglein immunization [7]. The commonest subcircle is characterized by IgG-mediated autoimmunity and is composed of:

- pemphigus foliaceus (PF) circle (PF, endemic PF, sebaceous PF, and PF herpetiformis, paraneoplastic pemphigus, drug-mediated PF showing PF-indicative autoantibody profile),

- pemphigus vulgaris (PV) circle (mucosal-dominant PV, mucocutaneous PV, pemphigus vegetans, and paraneoplastic pemphigus, PV herpetiformis, drug-mediated PV showing PV-indicative autoantibody profile),

- pemphigus as a part of multiorgan autoimmunity syndrome,

- pemphigus shifting inside one circle or between circles,

- PV/PF-coexistence cases,

- paraneoplastic pemphigus (PNP) with neither anti-DSG3 nor anti-DSG1 antibodies [1].

A model disease for pemphigus circle and the commonest clinical type of pemphigus is PV. This life-threatening chronic/acute ABD affects the mucocutaneous surfaces significantly debilitating quality of life [5]. The onset age is 40-60 years, and incidence ca. 0.7 per 100,000 persons [5,8]. Blistering in PV appears at suprabasal level as an effect of tissue-bound and serum IgG-driven autoimmunity against keratinocyte cell-surface antigens of aforelisted cadherin superfamily [9], with desmoglein 3 (DSG3) as the main autoantigen. The disease starts initially affecting oral mucosa (50-70%), that may remain the only site involved, yet extraoral lesions may occur simultaneously. Intraepithelial blisters evolve into aching erosions and ulcers. Predilection sites include face, parietal region of the scalp, sternal and interscapular regions of the trunk, intertriginous sites (umbilicus, interdigital spaces, scrotum, inguinal and axillary folds), scars and skin appendages – nail apparatus, hair follicles [1] and areas with transitional epithelium, what could be explained by the change of desmoglein expression pattern.

Histologically, suprabasilar blistering may be observed, whereas direct immunofluorescence study (DIF) of perilesional skin/mucosa depicts IgG (mainly IgG4) pemphigus-type deposits of fishing net pattern in intercellular spaces of the lower epidermis [1]. With virtually no invasiveness, direct immunofluorescence study on a plucked scalp hair (hDIF) may serve as a good alternative for DIF, visualizing pemphigus IgG, IgG1 and IgG4 deposits in outer root sheath of hair follicle even in patients without cutaneous lesions [10]. Still used, indirect immunofluorescence (IIF) test for presence of pemphigus IgG circulating autoantibodies is regarded historical method and is widely replaced with molecular studies e.g. ELISA, enabling assessment in serum, saliva or blister fluid [11].

PF, the less common pemphigus circle condition, usually affects the skin of the face, scalp and trunk, but may generalize. The disease is characterized by autoantibodies binding DSG1, that participate in blister formation at superficial level (granular layer). Although blister is a primary PF lesion, it is hardly ever seen, as it rapidly evolves into crust-covered erosions [1,5]. Interestingly, as main PV DSG3-antigen (130kDa) and PF DSG1-antigen (160kDa) differ, that corresponds with different blistering subtype and clinical features [5].

Concerning association with malignancy, PNP resembles clinically and histologically features of PV and erythema multiforme [5]. However, it differs in autoantibody profile. PNP autoantibodies may target simultaneously multiple antigens – desmoplakin I and II, BP230, periplakin, envoplakin, plectin, 170kDa protein, desmoglein 1 and 3, desmocolin familly, and many yet unknown proteins. PNP-type intercellular deposits can be visualized in IIF on transitional epithelium of rat bladder. Circulating autoantibodies affects not only mucocutaneus epithelium, but may bind organ-specific antigens of gastrointestinal tract or bronchioli – e.g. causing non-reversible and life-threatening constrictive bronchiolitis. Although rare, PNP is characterized with very high mortality [12].

2.2.2. Subepidermal autoimmune blistering dermatoses

Subepidermal ABD circle consists of chronic bullous diseases with autoantibodies binding mostly structural proteins forming DEJ:

- Bullous pemphigoid (BP) circle (urticarial BP, BP herpetiformis, sebaceous BP, erythrodermic BP, BP vegetans, pretibial BP, prurigo-nodularis-like BP, trauma-induced BP, pemphigoid gestationis (PG), lichen planus pemphigoides (LPP), lamina lucida-type linear IgA bullous dermatosis),

- Mucous membrane pemphigoid (MMP)/cicatrical pemphigoid,

- Pemphigoid Brunsting-Perry,

- Epidermolysis bulosa acquisita (EBA) circle (EBA, bullous systemic lupus erythematosus, sublamina densa-type linear IgA bullous dermatosis),

- Linear IgA bullous dermatosis (LABD) (non-EBA circle LABD, non-BP circle LABD),

- anti-laminin gamma1 pemphigoid (former anti-p200 pemphigoid) [1].

BP circle, the commonest ABD, is characterized by heterogeneous clinical patterns. However, it has common molecular feature – autoimmunity to extracellular, non-collagenous NC16A domain of BP180 antigen (BPAG2, collagen XVII alpha1) [1,5,13] and less often BP230 (BPAG2e, protein belonging to plakin family) [1,5]. It begins as a moderate pruritus, papular lesions or urticarial plaques developing in months into chronic bullous eruption characterized by well-tense blisters containing either serous or sanguineus fluid. The localized/generalized lesions may be oval or round, and rupture easily over time [5]. The arciform or serpiginous pattern they present is sometimes described as string of beans or cluster of jewels. Diverse symptoms are consequence of targeting different epitopes of these components of hemidesmosome adhesion complex. It affects often elderly people in their 60's-90's [1,5] with incidence of ca. 4.3 per 100,000 persons [8].

2.2.3. Other, vaguely characterized, autoimmune blistering diseases

There are also other autoimmune blistering diseases e.g. ABD with autoimmunization to IQGAP1 protein, erythema multiforme with anti-desmoplakin 1 and anti-desmoplakin 2 antibodies, linear IgM gestationis dermatosis, linear IgM dermatosis with IgM gammapathy and others that cannot be fitted into above categories, yet these are isolated cases with unknown relation to malignancy.

2.3. Malignancies associated with ABD

The issue of association of malignancy and ABD causes much controversy among researchers. WHO reports from 2008 indicated, that the 13% of death worldwide is caused by cancer, being the major cause of death with toll of 7.6 million people per year [14]. Neoplasms are heterogeneous group of entities characterized by rapid creation of abnormal cells that grow beyond their usual boundaries, and which can then invade adjoining parts of the body and spread to other organs [14]. The leading malignancies worldwide are lung, breast, colon, stomach and prostate cancers [15]. Several malignant tumors were reported in association with ADB, including lymphoproliferative disorders (Castleman's tumor, non-Hodgkin's lymphoma, chronic lymphocytic leukemia), lung, gastrointestinal, prostate, ovarian, endometrial, breast, bladder, renal, laryngeal, pancreatic cancers, thymoma and follicular dendritic cell sarcoma [16–22].

As ABD are relatively rare/regarded as rare conditions, there is limited data covering the association with other diseases. Japanese retrospective study on malignancy in patients suffering from pemphigus and pemphigoid observed incidence of 5.0% and 5.8% respectively [17], whereas lesser studies set these numbers as 11.2% and 10.4% [16]. The association ratio of malignancy with pemphigus increases by age, while no such correlation is found in pemphigoid. No gender-predisposition in ABD was reported in these patients [16]. Interestingly, lung cancer was most common in pemphigus and gastrointestinal tumors (gastric cancer in particular) in bullous pemphigoid [17]. Moreover, age-dependent malignancy-association in PV patients under (6.5%) and above 60 years (15%) should not be omitted [16]. Studies on BP and malignancy did not reveal age-correspondence [23].

As far as anti-enzyme ABD is concerned, association of DH with subsequent development of lymphoma seems well-documented [18,24,25]. It is possible that gluten intolerance is the factor associated with malignancies. Some data suggested, that following a strict gluten-free diet is protective against malignancy [26]. Moreover, researchers postulate that the risk of malignancy decreases with time from diagnosis of gluten-sensitive enteropathy to nearly the same as occurs in the general population. In light of above, it is postulated that the increased risk of malignancy in patients with DH may be the result of a polyclonal stimulation of lymphocytes by gluten that causes transformation into a malignant clone [18]. Still, in our over 20 years of clinical/laboratory experience as a clinician/clinical researchers we do not recall a DH-associated lymphoma patient.

There is a wide group of malignancies concomitant with ADB. Lung cancer has been reported in coexistence with wide range of ABD: PV [17,27,28], PNP [29], pemphigus vegetans [30,31], pemphigus herpetiformis [32], IgA pemphigus [33], BP [34] and MMP [35]. In some BP cases, tumor resection led to complete recovery [36] supporting the thesis of close interrelation of the diseases. Gastrointestinal tumors have been reported in association with BP [17,37], PNP [38], pemphigus vegetans [39], PV [40–45] and MMP [46] sometimes with post-excisional remission [47,48]. Both chronic leukemia and lymphoma have been reported with DH [49–51] and PNP [52–54]. Based on few case reports, MMP [55–57] is not rare finding in leukemia. There has been only one case of BP reported in patient with leukemia [58]. Thymoma and PV appears in numerable patients [43] with post-excisional remissions not uncommon [59]. Among reported thymoma-related ABD, there are also cases of PF [60,61], BP [62] and MMP [63]. Malignant tumor of the pancreas seem to be generally connected to MMP [64,65] and sometimes PNP [66]. Renal neoplasm has been reported to occur in with BP [67–70] and occasionally with MMP [71], PNP [72] and PF [73]. Ovarian cancer was incidentally described in relation with BP [74], anti-laminin gamma1 pemphigoid [75] and MMP [76]. Concerning prostatic cancer, single cases of PNP [77], pemphigus herpetiformis [78], PF [79] and MMP [80] were described in literature. There are numerous case reports on ABD and breast cancer including predominantly BP [20,81–85] and PV [86,87] with well-documented BP-lesion induction with radiotherapy.

3. Endogenous factors leading to breakage of self-tolerance in malignancy

Endogenous factors seem to be crucial for development of autoimmunity, as they form the organism reaction to external threat.

3.1. Development of paraneoplastic immunity

The autoimmunity in cancer is developed by distortion of immune system, arising from central tolerance disruption, peripheral immunity rearrangement and altering of self-antigens. Cancer-associated impairment of the function of immune system may take place at many stages. Rearrangement of T-cell receptor (TCR) genes proceeding in thymus cortex promotes T-cell education to recognize major histocompatibility complex (MHC) molecules of self-cells. It is a necessary condition for a T-cell to pass the positive selection process. The negative

selection, being the following stage, is conducted in thymus medulla, where T-cells are exposed to plethora of tissue specific self-antigens (TSAs) by medullary thymic epithelial cells. Self-antigens presented to T-cells are previously processed, thus some T-cells expressing TCR with high affinity to poorly presented antigens may evade negative selection achieving maturation [88]. The process is controlled by autoimmune regulator (AIRE) transcription factor [89]. Autoaggressive thymocytes are being terminated in apoptosis. Impairment of any of these stages – positive selection, negative selection, antigen processing, antigen presentation by malignancy, might have impact on T-cell set and scope of activity in periphery. Thymoma is the most common neoplasm of thymus, outrunning lymphomas, germ cell tumor, thymic carcinoma, carcinoid tumors and others [90]. One of the syndromes in relation to thymoma is paraneoplastic pemphigus, where diverse autoantibodies target diverse structural autoantigens. While pemphigus vulgaris (PV) and paraneoplastic (PNP) pemphigus may both target the same antigen, the difference is within the range of them and difference in epitopes bound (e.g. mucocutaneus PV preferably targets DSG3 N-terminal determinant, while PNP binds multiple epitopes). Another distinctive feature is IgG subclass – predominant PV IgG autoantibody subclass is IgG4, while in PNP – subclass is IgG1 and IgG2 [1].

Some authors hypothesized that tumor cells alone may produce the autoantibodies [91,92]. The thesis of in-tumor immature T-cell improper maturation, without negative selection, leading to autoaggression may be supported by findings in patient with follicular dendritic cell sarcoma [93]. Malignancy is based on breakage of cell cycle guarding and dysregulation of gene expression resulting in over- or underexpression of proteins. Via gene mutation, the neoplastic cell changes the antigen suit, by exposing altered self-antigens or "hiding" those already known. The reaction of immune system to cancer growth is immune cells recruitment (T-cells, NK cells, mast cells) and inflammation by various mediators causing apoptosis of both neoplastic and non-neoplastic cells. One T-cell can recognize many antigens presented by different MHC molecules. The condition of recognition is the compatibility of antigen fragment with lymphocyte TCR. Along with antigen sequestration theory, the determinants of cell proteins released in tumor necrosis can be exposed by antigen presenting cells to matured T-cells that migrate to lymph nodes. B-cells in response start to produce polyclonal antibodies against novel tumor epitopes. However, T-cells may also react with cancer antigens starting the chain of events leading to production of certain antibody cross-binding both neoplastic antigens and self-antigens [90].

The role of immune system protection against malignancy can be exemplified by noticeable higher cancer incidence in patients given immunosuppressive drugs impairing self/foreign-antigens recognition. Hence hypothetically, the distortion in immune system function in ABD may contribute to further susceptibility to the development of malignancy. Naive T-cell activation in the periphery alone is thought to be insufficient for autoimmunity induction and co-stimulation by CD28, a co-stimulatory molecule activating T-cells, seem to be necessary [94]. CD28 is able to bind CD80 molecule and CD86 molecule, constitutionally expressed on B-cells, subsequently enhancing IgG antibody production [95]. CD80 molecule appear also scantly on other antigen-presenting cells (APC – primarily B-cells, macrophages and dendritic cells) and is upregulated after APC activation. Active APC present CD40, a ligand for CD40L expressed

on active T helper cells. Ligation of CD40 on APC cells leads to increase co-stimulatory capacity and antigen presentation ability enhancement. It is worth noticing that, CD80/CD86 is also expressed on cells of diverse lymphomas (e.g. non-Hodgkin lymphoma and chronic lyphocytic leukemia), that can act on behalf of APC, evading being recognized by the immune system. It was suggested that T-cells may omit the "APC guarding stations" in lymph nodes and directly infiltrate the tumor. Thus, the tumor itself may act as a "T-cell kidnapper" and support naive T-cell infiltration, activation and differentiation into effector cells [96], hypothetically programming or "indoctrinating" T-cells to achieve autoimmune potential. Moreover, the study based on collective incubation of non-malignant regulatory and cytotoxic T-cells with chronic lymphocytic leukemia cells showed non-malignant T-cells cytoskeleton remodeling decrease and vesicle trafficking decrease resulting in impaired synapse formation [97,98].

Fc receptors (FcRs) play essential role in the activation/inhibition of various cells in antibody-mediated immune responses. Thus, FcRs function may be a key purpose in the treatment with monoclonal antibodies (mAbs) therapy. Probably, FcRs may be a molecular link between ABD and malignancies [99,100]. FcRs-targeting therapies are used for ABD and cancer, e.g. rituximab, which is used in ABD and is the first anti-tumor mAb drug admitted by the US Food and Drug Administration. It was demonstrated that Fc-receptor-dependent mechanisms contribute substantially to the action of cytotoxic antibodies against tumors and indicated that an optimal antibody against tumors would bind preferentially to activation Fc receptors and minimally to the inhibitory partner FcγRIIB [101]. Interestingly, rituximab – the chimeric monoclonal IgG1antibody specific for the B-cell marker CD20 – was recently approved for the treatment of B-cell lymphoma. In vitro studies with rituximab have indicated that a direct pro-apoptotic activity may be associated with this antibody [102].

3.2. Genetic predisposition

There seems to be a causative relation between HLA-association and autoimmunity in ABD, especially in pemphigus [103–109] and pemphigoid [110], yet these observations may vary geographically. HLA-DQB1*0301 allele, associated with MMP [111–114], was reported in patients with esophageal squamous cell carcinoma [113], gastric cancer [115], HPV-associated cervical neoplasia [116]. It was hypothesized, that the gene may have a role in T-cell recognition of basement membrane antigens resulting in production of IgG autoantibodies binding basement membrane antigens [117]. It is also possible, that the link exists between certain malignancies and HLA or autoimmunity predisposition connected to defective apoptotic genes. Nonetheless, there are few studies covering that field, so coexistence may also be purely coincidental.

3.3. The role of cytokines

There is eventuality of oversecretion of certain cytokines regulating the mRNA expression and polarization of certain T helper (Th) cell population [118,119], as the most common neoplasms in relation to ABD seem to be lymphoproliferative malignancies. It has been reported that qualitative as well as quantitative alterations in cytokine production can result in activation of inefficacious effector mechanisms and therefore, complex and severe impairment in immune

functions [119]. Polarization to Th1-mediated immunity via IL-1, IL-4, IL-5, IL-6, IL-8 and IFN-gamma was observed in BP [120], while Th2-mediated reaction via IL-10 and IL-4, in conjunction with decrease in IL-2 and IFN-gamma levels, were shown in PV [119]. The cytokines that promote cancer growth (e.g IL-8 for colon and gastric cancer) [121,122] may collaterally initiate Th population shift to the profile promoting ABD. Likewise, a proliferation inducing ligand (APRIL) of TNF family plays an important role in several autoimmune diseases, including ABD, and in several malignancies. Soluble APRIL level was reported to be raised in e.g. lung, thyroid, lymphoid and gastrointestinal tumors [123,124], thus supposedly contribute to dysregulation of immunity in cancer. B-cell activating factor (BAFF/BLyS), belonging to TNF family, regulates B-lymphocyte proliferation and survival, also in B-cell lymphoproliferative disorders [125]. Interestingly, serum of BP-, but not PV-patients, showed high titers of BAFF [126]. It seems rational, that molecular mechanisms leading to increase of BAFF level in BP patients may favor pathological lymphoproliferation.

3.4. Sex hormones

As some entities of ABD have sex-predisposition, just as some malignancies, the role of sex hormones on development of MAABD need to be investigated. Certain tumors prevail in female (breast cancer, non-Hodgkin lymphoma), in man (gastrointestinal tumor, laryngeal cancer, Hodgkin lymphoma or kidney cancer) or are typical for one sex for anatomical reasons (prostate cancer, ovarian cancer) [15]. Sex-associated distribution of PV and BP seems equal with slight female dominance, while other ABD promote males (DH – 2:1) or are exquisitely female domain (PG) [5,127]. Both T and B cells have estrogen, testosterone and prolactin receptors. Furthermore, androgens and estrogens have an impact on the Th1/Th2 balance [128]. Therefore, menopause may be followed by change in cytokine profile affecting immune response. Interestingly, studies on endocrine hormones in PV- and BP-patients have revealed increased serum levels of both adrenocorticotropic hormone (ACTH) and hydrocortisone [129]. It was hypothesized, that slight female predominance of women in PV may be contributed to hormone replacement therapy (HRT) [130]. HRT is known risk factor for ovarian cancer, yet the impact on neoplasm induction in breast cancer and endometrial cancer is uncertain [131].

4. Exogenous factors: Epitope spreading and bystander effect

Multiple exogenous factors of diverse origin may contribute to trigger MAABD, e.g. drug-induction of malignancy in ABD patients and, contrarily, self-antigen drug/virus/bacteria-induced alteration. Drug-induced immunosuppression in ABD (e.g. with methotrexate) was considered a prospective triggering factor for lymphoproliferative disorders [132]. Viral/microbial factors could serve both as a trigger for autoimmunity and risk factor for malignancy. It was hypothesized, that foreign antigens (e.g. viral, fungal, bacterial) may act as a superantigen in ABD induction or take part in epitope spreading phenomenon [133,134]. HBV, HCV, H. pylori, T. gondii and CMV were reported to contribute to elicit ABD [135]. Viral infection (TTV, HSV2, HHV6, HHV8, HSV1, HSV2, EBV, HBV, HIV-1, Coxsackie virus) [136–143] has

been put forward as a causative agent of ABD-type autoimmunity in PV, PF, BP and pemphigus vegetans. There has been multiple factors suspected of prostatic cancerogenesis, including viruses (BK, HSV2, HSV6, HSV11, HSV16, HSV18, HSV31, HSV33, HHV8, XMRV, CMV) and microbial agents (Chlamydia trachomatis, Mycoplasma hominis, Ureaplasma urealyticum, Neisseria gonorrhoeae and Treponema pallidum), yet data was inconclusive or supported no relation [144–151]. Surprisingly, Epstein-Barr virus infection has been found statistically associated with increased breast carcinoma risk [152]. It was speculated that the virus itself may play a role in ABD induction [153,154]. The data covering the issue of exogenous factors contributing to both malignancy and ABD is yet generally inconclusive.

Constant activation of immune system in ABD sustains chronic inflammation leading to tissue degeneration by proinflammatory molecules. As a result, the risk of the neoplasy increases [3]. However, that relation could be two-sided. Inflammation in tumor nest stimulates and modifies the immunity mechanisms. Furthermore, there is a hypothesis that the multiplicity of target antigens in ABD may result from intra- and intermolecular epitope spreading. The effect of epitope spreading in ABD is well-known fact and it seems to be a constitutional compound of autoimmunity. Structural similarities between autoantigen epitope and to-be-autoantigen epitope may lead to production of autoaggresive cross-reacting immunoglobulins [9,155]. This phenomenon, which represents a broadening of the immune response from a single epitope to additional epitopes, is also described in cancer and recent findings suggests that epitope spreading may be a more significant predictor of effective immunity [156].

The initial anti-cancer immunity may ricochet to autoaggresion by epitope spreading and bystander effect alike [157]. Local inflammation in the course of malignant tumor or chemotherapy/radiotherapy treatment may result in enhanced autoantigen presentation that causes T-cell priming, activation and expansion of additional specificity [158]. Therefore, in situations where immunosuppressive/anti-cancer treatment is absent or ceased, anti-cancer response may be responsible for development of autoimmunity to self-antigens characteristic for ABD.

5. Molecular mechanisms: The possible connection between malignancies and ABD

ABD are characterized by autoantibodies against structural proteins of the skin, including molecules of dermal-epidermal junction and desmosomes. Cancer progression is a complex and multi-step process in which components of DEJ as well as a desmosomal molecules play a pivotal role in the development of metastasis. Probably, more than 90% of human cancers are of epithelial origin [159] and the autoimmunity against epidermal structures may play important role in those carcinogenesis. Thus, probably DEJ/desmosomes is the first barrier in tumor cells invasion. In light of this, understanding the molecular basis of pathological autoinflammation induction in autoimmune blistering dermatoses in relation to the mechanisms of malignant transformation is paramount for early detection and treatment of epithelial-derived cancers [160]. However, the precise molecular mechanisms underlying the association of malignancy with ABD still remain unknown. Nevertheless, understanding the

link between the production of pathogenic autoantibodies in ABD and the development of the associated neoplasy should facilitate the development of more specific diagnostic tests and therapeutic strategies [160].

5.1. Malignancy in relation to the autoimmunity in pemphigus group: The role of desmosomes components

Pemphigus group is characterized by presence of autoantibodies against desmosomal cadherins. Research on human and animal models indicated that alternation in desmosomes components may lead to tumor progression and metastasis. However, little is known about the role of desmosome during cancer development [161]. It is clear, that the origin and maintenance of epidermis requires the coordinated regulation of proliferation, adhesion, migration and differentiation. Conceptually, desmosome complexes form when desmosomal cadherins – DCs (desmogleins – DSGs and desmocollins – DSCs) participate in heterotypic interactions that bring the plasma membranes of adjacent cells in close apposition [161]. The cytoplasmic tails of these cadherins interact with plakoglobin and plakophilins.

The data describing desmosome protein expression during human cancer progression are conflicting [161–163]. Molecular abnormalities of desmosomal proteins (DPs) are observed in ABD and epithelial malignancies. However, in malignancy, where cells may separate, detach and metastasize, it is possible that alterations in DPs expression may be the reason of carcinogenesis process. Several studies demonstrated that downregulation of DCs occurs during the progression of cancers and is often correlated with and predictive of tumor metastasis [161,162]. On the other hand, other studies reported overexpression of DCs during the cancer progression, and this pattern is associated with poor prognosis [163]. The regulatory mechanism controlling DCs expression are scanty explained. As known, gene expression may be modulated by genetic and/or epigenetic mechanisms and in this way may contribute to the development of pathologic autoimmunity or malignancies. Genetic changes as mutation, deletion, and gene rearrangement of DCs have been poorly found in cancer and ABD. Possible mechanism may also involve post-translational modification of protein, like phosphorylation, acetylation or methylation. In light of this, some data reported methylation of DCs, e.g. methylation of DSC3 in breast cancer. It was showed, that DSC3 is downregulated in colorectal cancer by DNA methylation [164]. Thus, further analysis of methylation status of DCs DNA may be useful to predict clinical outcomes in patients with malignancy.

Alternatively, the possible link between desmosomal components and malignancy may be the Perp protein. The Perp tetraspan membrane protein was originally identified as a transcriptional target of the p53 tumor suppressor upregulated during apoptosis [161,165]. However, Perp may have function as a target of the p53-related transcription factor (p63) involved in maintaining epithelial integrity by promoting desmosomal cell-cell adhesion. Electron microscopy and biochemical analyses showed that the blistering phenotype observed in the Perp-deficient epithelia is accounted for by both a reduction in desmosome number and compromised desmosome complex formation. It is suggested, that pemphigus autoantibodies may trigger internalization of Perp, which enhances adhesion defects [166]. Perp's position downstream of p63 and p53, as well as its essential role in normal desmosome function, suggest

that it may be a target for mutation in human blistering diseases or cancer [167]. An interesting issue remains why a p53 target would play such a prominent role in adhesion in the skin. It was suggested [167], that this role relates to Perp being a key component of the transcriptional program for stratified epithelial development and maintenance specified by the p53 family member p63. Perp is a transcriptional target of p63 during development and in mature mouse skin [168]. Beyond a role in epithelial function, Perp's status as a p53 target involved in apoptosis may suggest a potential role as a tumor suppressor. Given that loss of both p53 and p63 cooperate in tumorigenesis, loss of Perp similarly may be expected to promote cancer development in some context. The future analysis of Perp will provide new insight into the role of desmosomes in epithelial homeostasis and cancer [167]. It was disputed, that Perp-deficiency promotes cancer by enhancing cell survival, desmosome loss and inflammation, and fundamental role for Perp and desmosomes in tumor suppression [161]. Interestingly, it seems that DSC3 is a p53 response gene and addition of wild-type p53 was found to be sufficient to induce expression of DSC3 in breast cancer [169]. Thus, it was of great interest to investigate whether this pathway is also active in tumor cells. In light of above, the induction of p53 may have impact on expression of DCs [164].

Malignancy may be also associated with pemphigus group via pemphigus-antibodies-induced signaling pathways. Thus, cadherins expression can function as a tumor and invasion suppressor due to its participation in processes such as morphological differentiation and contact inhibition of growth and motility. Several different molecular mechanisms for perturbation of cadherin function in epithelial tumors are reported: (i) transcriptional or genomic regulation of cadherin expression, (ii) mutations (e.g. deletion, insertion) of cadherin or catenin genes and (iii) regulation of adhesive function by signaling pathways. A signaling cascade initiated by pemphigus vulgaris antibodies may results in reduced availability of plakoglobin and abrogation of its function as transcriptional repressor of the proto-oncogene c-Myc. This in turn results in accumulation of c-Myc. Moreover, c-Myc expression is commonly upregulated in tumors. There is also evidence, that etiology of some skin cancer (e.g. BCC) may be dependent on several signaling pathways [170], which can be shared with pathological autoimmunity induction in pemphigus group. Other signaling pathways may engagement of Src, Wnt, hedgehog, epidermal growth factor receptor (EGFR) kinase (EGFRK), cAMP, protein kinases A and C (PKC), phospholipase C, mTOR, p38 MAPK, JNK [166]. Especially, it is postulated that DSG3 is a key player in Src signaling and overexpression of DSG3 elicited a phenotype similar to this with increased Src activity. Interestingly, this phenotype may be observed in some kind of cancers (e.g. SCC) [171]. Moreover, it is estimated that 35% of cancers show increased MAPK activity [172]. On the other hand, MAPK is involved in the process of acantholysis in pemphigus group.

Furthermore, some data [173,174] demonstrated possibility that switching of DCs could play an important role in the development of some kind of cancer. Tumor development is in part characterized by the ability of cells to destruct of cell-cell adhesion and invade the surrounding tissue. Perhaps, the disturbances in desmosomal cadherin (as DSCs) expression could affect beta-catenin signaling [174]. It is known, that increased beta-catenin signaling is a common causative event in some kind of cancer (e.g. colorectal cancer), thus desmocollin switching

could play a contributory role in the initiation of early stages of cancer. In light of this, the evidence that altered expression of desmosomal proteins in various human malignancies has been accumulating.

5.2. Malignancy in relation to the autoimmunity in subepidermal blistering dermatoses: The role of the DEJ proteins

Pathogenesis of blister formation in subepidermal blistering dermatoses is associated with destruction of dermal-epidermal junction and anchoring fibers. Recent studies shown interesting function of the hemidesmosome (HD) components in signal transduction, involving effect on cell behavior in tumor invasion [175]. Data indicated altered expression of DEJ proteins at different stages of carcinogenesis, what may suggest the association between tumor progression. Aberrant expression of DEJ proteins, which are associated with subepidermal blistering dermatoses (e.g. BP180, BP230, alfa6beta4 integrin, laminin-322) in epithelial cancers was demonstrated, what may indicate their role in tumor development and invasion [175]. Reduced expression of HD components may results in the detachment of cells from the basement membrane, facilitating piling or migration of cells [176]. On the other hand, carcinoma cells may upregulate the expression of HD molecules to enhance the attachment capacity of metastatic cells to the DEJ at the metastatic site in order to establish metastatic growth.

The aberrant expression of DEJ component may reflect dysfunction of HD, that occurs as an early event in multistep carcinogenesis of epithelium [177]. Downregulation of BP180 – one of the major autoantigen in bullous pemphigoid – was found in basal cells in mild dysplasias, upregulation of BP180 in suprabasal keratinocytes in moderate and severe dysplasis as well as in the central cells of squamous cell carcinomas (SCC; G2 and G3) using immunohistochemical (IHC) and in situ hybridization (ISH) methods [175]. Furthermore, this group of researchers indicated that overexpression of BP180 was found at the invasive front of the tumors. Authors suggested that reduced BP180 expression at the early step of carcinogenesis may reflect disturbed keratinocyte adhesion to the basement membrane. BP180 gene expression is significantly induced by a tumor promoter PMA [175]. Previous findings obtained by the same authors revealed reduced BP180 expression in the peripheral cells of carcinoma islands in solid and keratotic basal cell carcinomas (BCC) and in the basal cells of invading buds in superficial BCCs [178]. The altered expression of DEJ proteins is likely to coincide with the disassembly of HD, which is an essential step in keratinocyte migration and carcinoma cell invasion [175]. Moreover, downregulation of BP180 and other hemidesmosome components was previously detected in vivo in prostate cancer and in the invasive cells of ductal mammary carcinoma [179,180]. On the other hand, upregulation of HD components has been reported in a variety of SCCs [177,181]. It was argued that BP180 upregulation in carcinoma cells at the invasive front of malignant tumors is important in the carcinoma cell migration [175]. Other study described upregulation and altered distribution of BP230 and alfa6beta4 integrin in the areas of invasive growth of head and neck SCCs [181]. PMA is a potent tumor promoter capable of inducing several genes that have a role in carcinogenesis and tumor invasion [182]. It is known, that laminin-332 gamma2 chain gene promoter is one of the targets of PMA activation, occurring via interaction with the activator protein 1 complexes [183]. The

relationship of BP180 to malignancy is discussed. BP180 has possible phosphorylation sites and may by phosphorylated in SCC [177]. Enhanced expression and abnormal distribution of BP180 in various precancerous and cancerous tissues was revealed, including e.g. SCCs and Bowen's disease [177].

As it was demonstrated that expression of BP180 was decreased or absent in cutaneous neoplasms [184], some authors speculated that some type of carcinomas itself might expose BP180 antigenic epitope, which would normally be hidden, thus inducing the production of autoantibodies that lead to the onset of BP [185]. It was proposed that BP180 neoexpression could be associated with early/malignant transformation of keratinocytes as widely expression of BP180 was demonstrated in SCC in contrast to normal skin, where this protein is restricted to basal keratinocytes [186].

Laminin-322 (previously named laminin-5) is the main autoantigen in anti-epiligrin cicatricial pemphigoid, mucouse membrane pemphigoid. Laminin-332 and alfa6beta4integrin may play an important role in tumor progression via activation of phosphatidylinositol-3 kinase signaling (PI3K) [187]. There was shown, that it is highly expressed in several types of squamous and other epithelial tumours [188]. Moreover, in these tumors, laminin-322 shows tendency to accumulate at the interface of the tumor with the surrounding stroma, and expression of this proteins correlates with tumor invasiveness [188]. Interestingly, keratinocytes from patients with junctional epidermolysis bullosa, that did not express laminin-322 or beta4integrin, showed a lack of tumorigenecity in immunodeficient mice after transformation [188]. Perhaps, the binding of collagen VII to laminin-322 may be essential for tumorigenesis [188]. Furthermore, the laminin-322-derived signaling is an important component of tumorigenesis. As mentioned above, constitutive activation of the PI3K pathway leading to RAC1 GTPase activation may be the triggering factor inducing tumor invasion.

6. Case reports of MAABD

As the association between ABD and malignancy is noted in many case reports, the question of causal connection is raised. There are three situations possible concerning the relation: i) malignancy preceding ABD, ii) malignancy coexisting with ABD, iii) malignancy following ABD. For a long months and years, many cases of ABD are undiagnosed, misdiagnosed and subsequently mistreated due to relative rarity and therefore low awareness of ABD and its symptoms. The time period elapsed between the first symptoms and diagnosis, makes the time-onset relation between ABD and cancer usually uncertain.

Here, based on our personal clinical/laboratory/research experience, we present a dozen of memorable/representative patients with association of malignancy, both cutaneous and internal, and ABD over the last decade. Unfortunately, usually there is no experimental data indicating if it is a random coincidence or cause-and-effect relationship in individual patient. Still, the diagnosis of such a concurrence increases mortality.

6.1. Anti-desmosomal autoimmunity circle / pemphigus group cases

6.1.1. Case 1 — Mucocutaneous pemphigus vulgaris / lung cancer

An elderly female with painful oral erosions, flat white-speckled infiltrations, mucosal edema and enlarged submandibular lymph nodes was admitted to oncology center outpatients. Histopathological examination of the retromolar mucosa of the left alveolar process of maxilla showed paraepidermoid epithelium with focal high-grade dysplasia and few neoplastic cells.

Due to improper biopsy technique full examination of the material was impossible. Therefore, the patient was readmitted to the oncology ward, with tentative diagnosis of carcinoma planoepitheliale with bilateral metastases to neck lymph nodes, for bilateral selective lymphadenectomy and probational excision of the lesions at right buccal region and left soft palate. Histopathological examination on probational biopsy showed mucous membrane fragments with features of basement membrane disruption and acantholysis. There was abundant infiltration consisting of lymphoid cells with plasmocyte prevalence and presence of granulocytes. The overall image did not support the diagnosis of carcinoma planoepitheliale, yet suggested pemphigus. Chest x-ray showed left-sided pleural effusion with costodiaphragmatic recess filling. At the posterolateral side of the lung, thin layer of liquid reaching 7th rib in the posterior axillary line was observed. Ultrasonography of the neck showed non-enlarged thyroid gland (10 ml of volume) with hypoechogenic node (11 mm x 8 mm) and 3 lesser hypoechogenic nodes of diameters up to 4 mm in the left lobe. Enlarged lymph nodes, with narrow lymph sinuses (up to 15 mm x 8 mm) and unclear character, were seen bilaterally in the upper part of the neck vessels beyond mandibular angles.

The patient was directed to dermatological ward for further diagnostics. Laboratory tests showed increased sedimentation rate. DIF of perilesional skin of the vulva revealed IgG(+), IgG1(++) and C3(+) deposits in the intercellular spaces of the spinous layer of epidermis. hDIF on pulled-out hair revealed IgG(+), IgG1(+) and IgG4(+) deposits in the intercellular spaces of the outer root sheath. DIF of larynx mucosa showed fragmented specimen, mainly without epithelium. There was fragmented epithelium consisting of several cells at the specimens margin (evident acantholysis) with surrounding noticeable IgG(+/-) and C3(+/-) deposits. IIF study on monkey esophagus revealed circulating IgG class of pemphigus-type autoantibodies against desmosomal proteins of keratinocytes – titer above 1/80. On the basis of abovementioned tests the diagnosis of mucocutaneous PV was reached.

After amelioration of the lesions, due to pulse steroid treatment, she was dismissed from the ward. Two months later, she suffered from aggravation of mucosal erosions, haematopnoe and dyspnoe. The woman was admitted to oncology center, where chest computed tomography (CT) scan visualized solid mass in the left lung (Fig. 1A). Via bronchofiberoscopy, carcinoma planoepitheliale of the left lung (G4) with hepatic metastases was diagnosed. Palliative radiotherapy (20 Gy/T) of the mediastinal/left pulmonary region led to aggravation of mucocutaneous PV (Fig. 1B).

6.1.2. Case 2 — Mucocutaneous pemphigus vulgaris / oropharyngeal cancer

A middle-aged man observed blisters localized in the interscapular region and the posterior aspect of the neck (Fig. 2B, C). Simultaneously, he suffered from excruciating sore throat and dysphagia. He was consulted by ENT-specialist and subsequently was directed to oncology center for further diagnosis and treatment. Histological material obtained during laryngological diagnostics revealed carcinoma planoepitheliale keratodes invasivum of the right palatine tonsil, soft palate and uvula (T3N2M0) with metastatic focus in lymph node (Fig. 2A). Therefore, the patient underwent excision of the lesion with bilateral modified cervical lymphadenectomy. Neck ultrasound imaging visualized hypoechogenic polycyclic tumorous mass (43 mm x 25 mm) associated with lower pole of parotid gland with numerous small satellite nodules of diameter up to 6 mm and dissolved reactive lymph nodes up to 7 mm of length. The patient was treated with Intensity Modulated Radiation Therapy (IMRT) – 6 MeV photons for 34 cycles (68 Gy/t). Due to lesions regarded as notable cutaneous radiation syndrome of the neck (II* according to EORTC/RTOG scale), the few last cycles were diminished by 1 fraction and postradiative topicals were applied. Interestingly, the bullous lesions exacerbated (Fig. 2D) and appeared on the thorax, abdomen and limbs (Fig. 2E). No mucosal involvement was present at that time.

Due to above symptoms, he was consulted by the dermatologist. Histology of the skin revealed suprabasilar separation and acantholysis in the upper epidermis (Fig. 2F). IIF on monkey esophagus revealed circulating IgG class pemphigus-type antibodies against desmosomal proteins of keratinocytes – titer 1/320. DIF on the perilesional skin of the back showed IgG(+), IgG1(+), IgG4(+++) and C3(+) deposits in intracellular spaces of lower layers of epidermis (Fig. 2G). DIF of the plucked hair showed IgG4(+++), IgG1(++), IgG(++) and C3(+/-) deposits in intracellular spaces of outer hair sheath (Fig. 2H). Performed tests supported the diagnosis of mucocutaneous PV.

Four months later, patient was admitted to dermatological ward with numerous blisters and erosions on the skin of the thorax, back, limbs and head. Reddish postradiative aggravated PV lesions, which healed later with aggressive immunosuppressive treatment, with marginal blistering notably limited to the anterior surface of the neck, showed no visible reepithelialization. Numerous painful erosions presented on oral mucosa disabling patient's feeding and resulting in 10 kg weight loss. ELISA study revealed the presence of anti-desmoglein 1 (DSG1) IgG of titer 130.34AU/ml (cut-off point 41AU/ml) and anti-desmoglein 3 (DSG3) IgG of titer >150AU/ml (cut-off point 40AU/ml). IIF performed on rat bladder did not reveal serum antibodies of paraneoplastic pemphigus (PNP) type. Consulting laryngologist described numerous erosions of buccal and oral mucosa, yet noticed no features of recurrence of malignancy. The case was reported in literature [189].

6.1.3. Case 3 — Pemphigus foliaceus / pseudomyxoma peritonei

An elderly female was admitted to dermatological ward with numerous erythematous plaques, blisters and non-healing erosions covered with crusts – on the scalp, trunk and limbs (Fig. 3A, B). Her medical history was significant for angina pectoris, angioplasty (PTCA) with
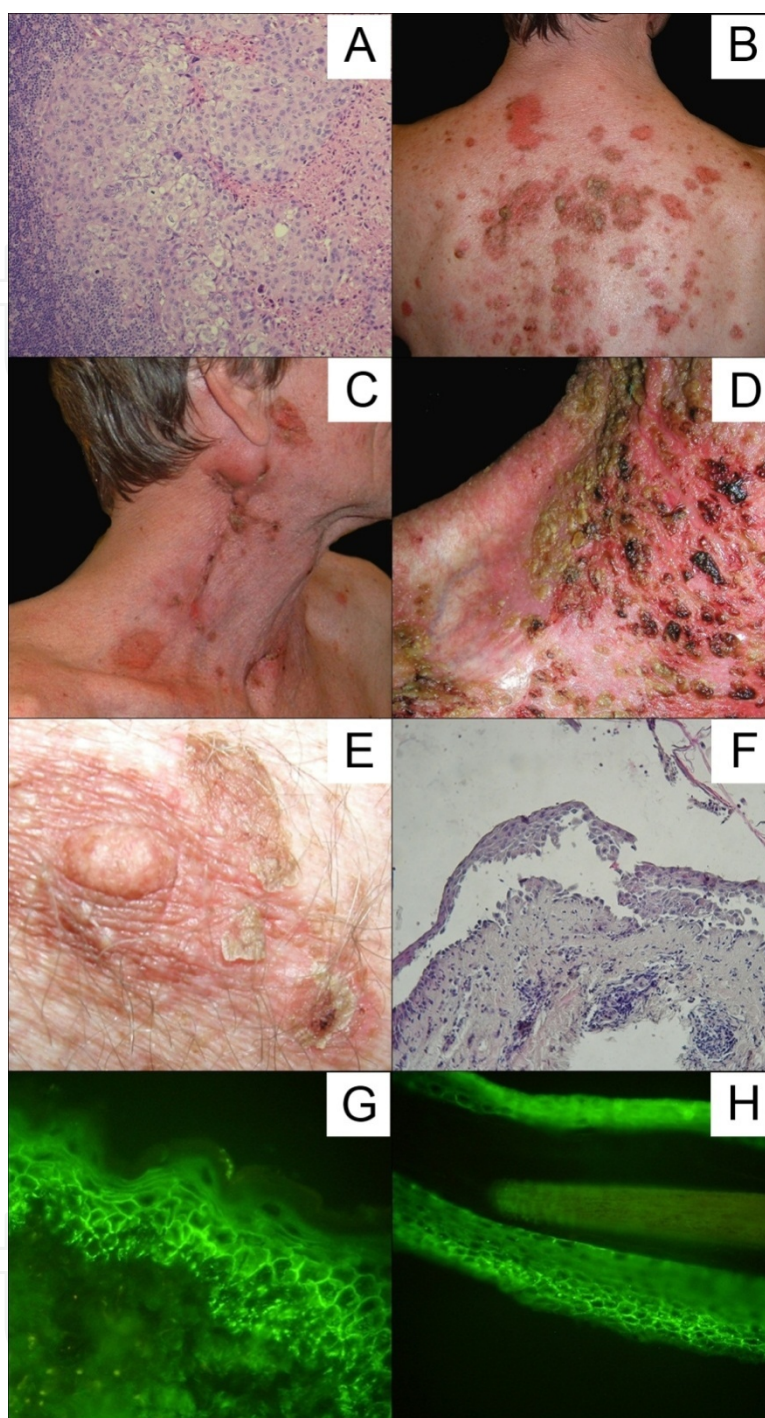
stent implantation due to myocardial infarction, hypertension, hypercholesterolemia, diabetes mellitus type 2, hiatal hernia and epigastric hernia.
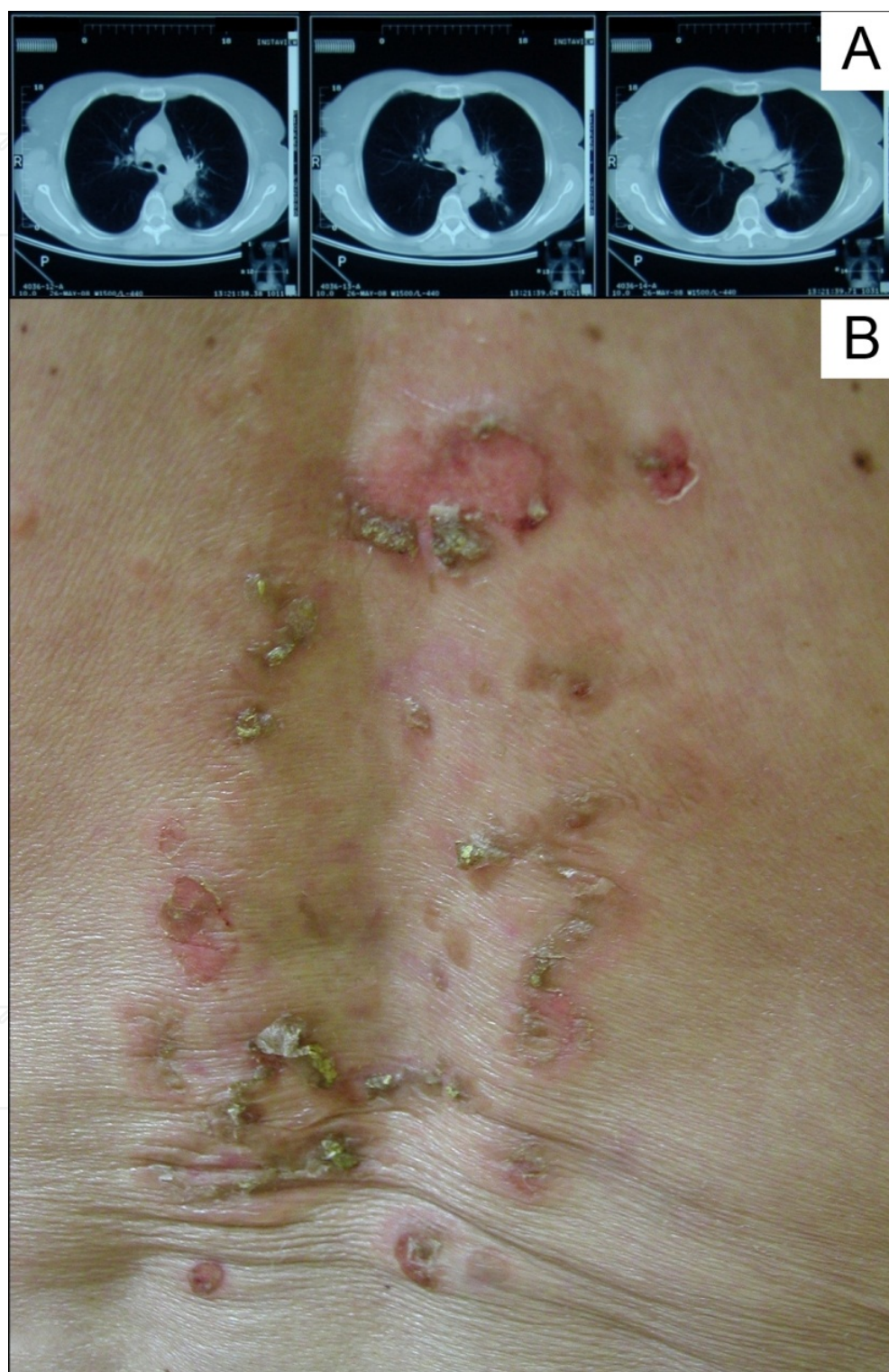
Figure 1. A. Chest CT of an elderly PV patient showing tumor in the left lung. B. Aggravation of mucocutaneous PV after palliative radiotherapy (radiotherapy-induced PV lesions).

Figure 2. A. Carcinoma planoepitheliale keratodes invasivum in lymphoid tissue. H+E staining. Courtesy of Prof. J. Bręborowicz. B. Numerous erosions on non-inflammatory skin of the back, some of them covered with brownish-greenish crusts. C. Erosions on non-inflammatory skin of the face and neck. Scar after the surgical excision of the cancer. D. Numerous merging erosions, some covered with bloody and greenish crusts on the skin of the neck area subjected to radiotherapy. E. Erosions covered with crusts around the nipple (a natural body orifice area). F. Suprabasilar separation and acantholytic blister in the upper epidermis. H+E staining. G. DIF of perilesional skin of the back: pemphigus IgG4 deposits in lower epidermis. H. DIF of plucked scalp hair: pemphigus IgG4 deposits in outer root sheath.

Initially, lesional skin sample examined by the cutaneous pathologist showed thin epidermis with fissures and flat vesicles in upper layer with slight acantholysis. Perivascular inflammatory infiltrates with prevalence of lymphocytes and eosinophils, focally involving the epidermis, were seen in the dermis. DIF test revealed deposits of IgG(+), IgG4(++) and C3(++) in intercellular spaces of epidermis. Marked acantholysis was visible and upper layers of epidermis were absent. Serum IgG, but not IgG4, autoantibodies of pemphigus type against desmosomal proteins of keratinocytes were present in IIF on rabbit labial mucosa and normal human skin, of titers respectively 1/40 and 1/160. The diagnosis of PF was made. She was treated with oral steroids and cyclophosphamide achieving remission before dismissal.

Six years later she was readmitted to dermatological ward due to aggravation of PF. IIF study on monkey esophagus showed serum IgG4 autoantibodies of pemphigus type against desmosomal proteins of keratinocytes – titer 1/80 (Fig. 3C). Abdominal ultrasonography revealed oval hyperechogenic solid mass (12 mm x 14 mm) in the middle part of the right kidney medulla suggesting kidney tumor. Two-phased abdominal CT scan visualized hypodensic well-delineated lesion (transverse diameter ca. 10 mm) in right renal medulla (suggestive of angio-myolipoma) characterized by density of adipose tissue, without contrast intensification.

The patient was supervised for years by dermatology practitioner. Due to increase of waist circumference, she was suggested to visit gynecologist. In gynecological control, the physician found right adnexal mass. The patient was directed urgently to gynecologic ward with tentative diagnosis of ovarian cancer, where she underwent hysterectomy with adnexotomy, omentectomy and appendectomy. The tumor was described by the histopathologist as low grade appendiceal mucinous neoplasm (pseudomyxoma peritonei) with metastasis to right ovary and omentum. Since then, she regularly visited gynecological oncologist.
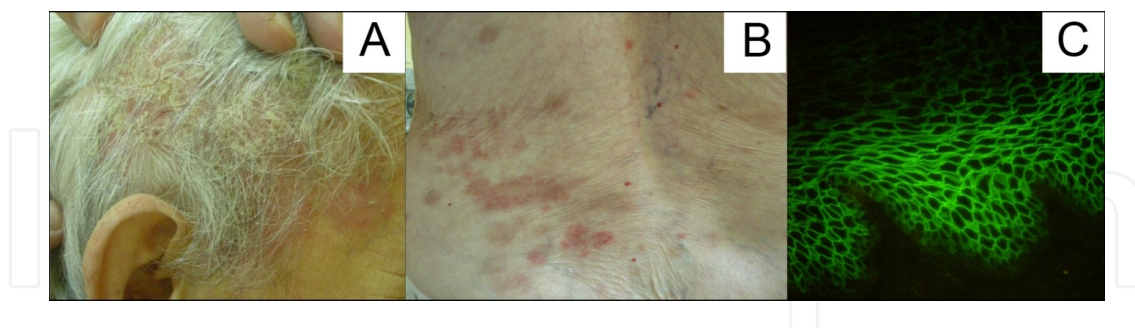
Figure 3. A. Erythematous plaques and crusts on the scalp of the head. B. Erosions and blisters on the back. C. IIF on monkey esophagus: pemphigus IgG4 autoantibodies. PF recurrence in the course of ACE-inhibitor treatment for myocardial infarction.

6.1.4. Case 4 — Pemphigus foliaceus / squamous cell carcinoma of the thorax

A middle-aged man was consulted by dermatological specialist due to disseminated erythematous plaques. The lesions were preceded by three months of uncomfortable itching on hands and feet. He was not diagnosed beforehand and was solely treated with topical steroids.

Therefore, he was directed do dermatological ward with tentative diagnosis of pemphigus/PNP for further diagnostics and treatment.

On admission, he presented erythroderma (Fig. 4A) and notable exophytic tumor on anterior surface of the thorax (c.a. 13 cm of diameter), clinically carcinoma verrucosum (Fig. 4B). Laboratory tests showed anemia, increased sedimentation rate and CRP. Histology of the perilesional skin showed marked acantholysis (Fig. 4C). Tumor margin bioptate showed clustered isles of atypic cells with fine keratin pearls giving overall image of highly differentiated squamous cell carcinoma (SCC) G1 (Fig. 4D). IIF on monkey esophagus proved the presence of serum IgG pemphigus-type antibodies against desmosomal proteins of keratinocytes – titer 1/160, yet IIF on rat bladder for serum PNP-type IgG was negative. ELISA test showed serum anti-DSG1 IgG level >200 RU/ml (cut-off point 20 RU/ml), yet did not revealed serum anti-DSG3 IgG – level 0 RU/ml (cut-off point 20 RU/ml). DIF of the perilesional skin visualized IgG(+), IgG1(++) and IgG4(++) deposits in the intercellular spaces of higher layers of epidermis and C3(++) deposits in the intercellular spaces of lower layers of epidermis (Fig. 4E). hDIF showed IgG(+), IgG1(+) and C3(+) deposits in the intercellular spaces of outer root sheath (Fig. 4F). With clinical and histological findings and molecular findings, the diagnosis of PF was made. After achieving dermatological improvement with doxycycline, antihistamine drugs and oral/topical steroids, patient was directed to oncology ward for SCC therapy.
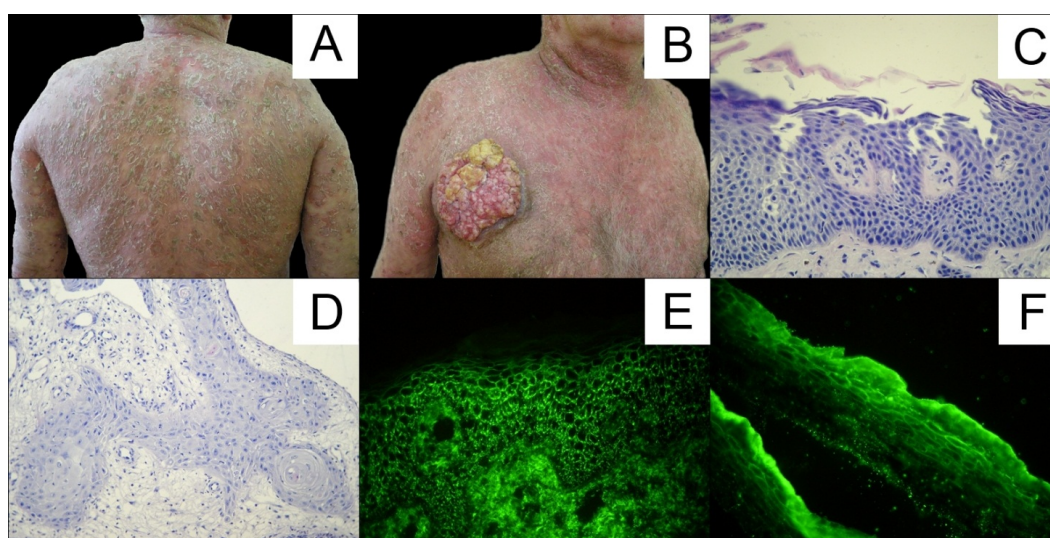
Figure 4. A. Disseminated erythematous plaques and crusts on the back. B. Exophytic tumor on anterior surface of the chest. C. Histology of the perilesional skin: Acantholysis. H+E staining. D. Histology of the tumor margin: Clustered isles of atypical cells with fine keratin pearls. Highly differentiated SCC. H+E staining. E. DIF of perilesional skin: IgG4(++) deposits in the intercellular spaces of higher layers of epidermis. F. hDIF of plucked scalp hair: IgG(+) deposits in the intercellular spaces of outer root sheath.

6.1.5. Case 5 — Mucocutaneous pemphigus vulgaris shifting from mucosal dominant form / lower lip squamous cell carcinoma

An elderly man treated for lower lip squamous cell carcinoma (SCC planoepitheliale keratodes; G2) that developed in lesions showing histological features of PV (Fig. 5E, F) suffered from

painful erosions on oral mucosa dating back several months (Fig. 5A). Subsequently, the blistering lesions and oozing erosions appeared on the skin (Fig. 5B, C). He called the dermatology professional and was directed to dermatological ward for diagnosis and treatment.

His laboratory tests showed increased sedimentation rate. Chest x-ray revealed fine atelectasis in the inferior aspect of the right lung. Ultrasonography of the abdomen showed non-echogenic area (16 mm x 18 mm) with intramural calcification and features of a cyst within VII segment and hypoechogenic lesion (dia. of 12 mm), probably angioma, in VI/VII segment of the of the right lobe of the liver. Two lesser cysts (up to dia. 5 mm) were found in left lobe. Gallstone (dia. 18 mm) was depicted in gall bladder, while right kidney showed sonographic features of hydronephrosis. An intravenous urogram (IVU) proved the presence of renal stone in right ureteropelvic junction, causing obstruction and dilatation of the pelvicalyceal system. In Tzanck test rounded acantholytic cells were present (Fig. 5D). Skin bioptate was characterized by the pathologist as PV material. hDIF showed IgG(++) and IgG4(+) deposits in intercellular spaces of outer root sheath (Fig. 5G). DIF on skin lesion margin showed IgG(+), IgG4(++) and C3(+) deposits in intercellular spaces of the lower spinous layer of epidermis (Fig. 5H). IIF on monkey esophagus revealed circulating IgG pemphigus-type antibodies against desmosomal proteins of keratinocytes – titer 1/320. ELISA test with patient's serum revealed serum anti-DSG1 and anti-DSG3 IgG class autoantibodies – levels respectively 133.81 RU/ml (cut-off point 41 RU/ml) and > 150 RU/ml (cut-off point 40 RU/ml). The diagnosis of mucocutaneous PV (shifting from mucosal dominant PV) was established. He was treated with pulses of high dose intravenous steroids combined with oral/topical steroids and doxycycline as a fundamental therapy with satisfactory effect.

6.1.6. Case 6 — Mucosal dominant pemphigus vulgaris / breast cancer

An elderly female, five years after right-side mastectomy due to breast cancer (invasive ductal carcinoma; G1; pT1cpN1Mx), was admitted to dermatological ward with painful non-healing erosions of oral and tongue mucosa. Her medical history was significant for diabetes mellitus type 2, arterial hypertension, diverticulosis, hemorrhagic gastritis and past episodes of deep vein thrombosis in the legs and thrombosis of the right central retinal vein. hDIF revealed IgG (+++), IgG1(++), IgG4(+++) and C3 deposits in intercellular spaces of outer root sheath (Fig. 6A). DIF on the perilesional mucosa showed IgG(+), IgG1(++), IgG4(+)and C3 deposits in intercellular spaces of lower layers of oral epithelium (Fig. 6B). IIF on monkey esophagus showed circulating IgG pemphigus-type antibodies binding spinous layer desmosomal proteins of keratinocytes – titer 1/160. Serum PNP-type autoantibodies were absent in IIF study on rat bladder transitional epithelium. ELISA study revealed elevated anti-DSG3 IgG level: 112.83 AU/ml (cut-off point 40 AU/ml), while IgG anti-DSG1 level was normal: 34.49 AU/ml (cut-off point 41AU/ml). Both laboratory tests and immunopathological findings supported the diagnosis of mucosal dominant PV. She was treated with oral methyloprednisolone, doxycycline and cyclophosphamide.

Because of her medical history, she was gradually deprived of methyloprednisolone, that resulted in an aggravation of PV within a month and need for urgent hospitalization. She was admitted with diffused erosions and blisters both on the skin and oral mucosa. Laboratory
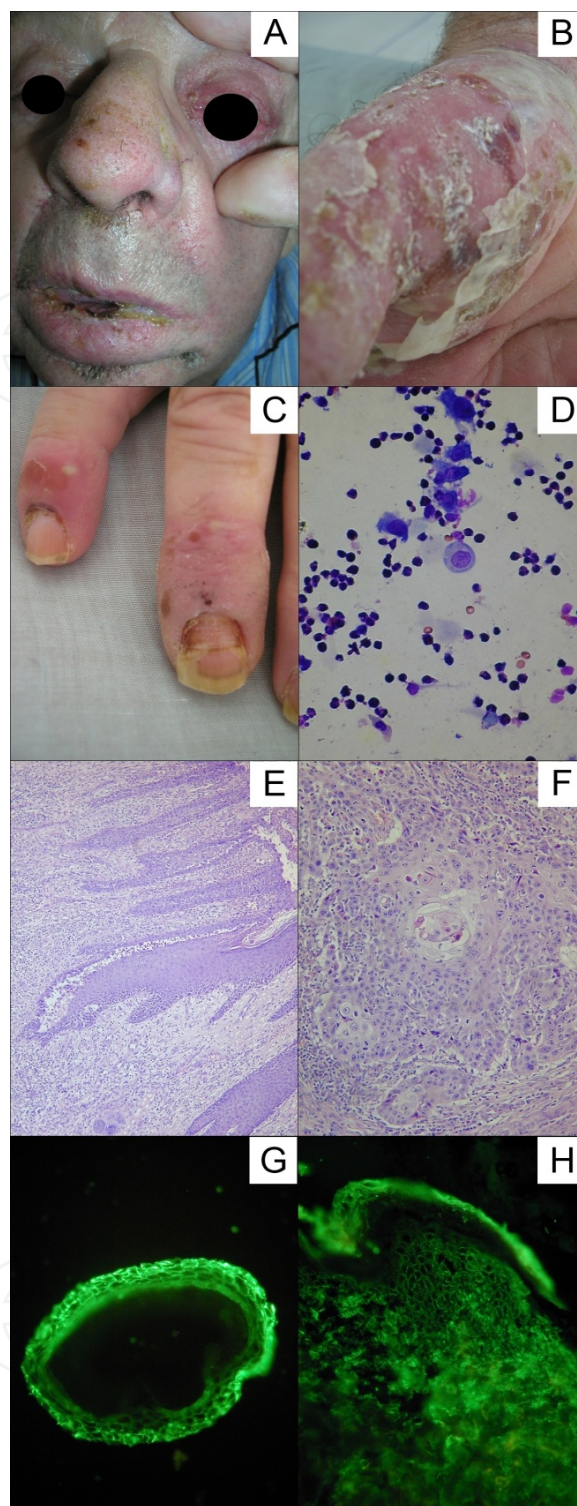
Figure 5. A. Mucosal erosions in patient with lower lip SCC and mucocutaneous PV. B. Fragile blister on the hand. C. Pemphigus vulgaris imitating paronychia. D. Positive Tzanck test: rounded acantholytic cells suggestive for PV. E. Suprabasilar cleft with acantholysis in the lower lip specimen showing also features of SCC. H+E staining. F. Lower lip SCC. H+E staining. Courtesy of Prof. J. Bręborowicz. G. hDIF: pemphigus IgG deposits in intercellular spaces of outer root sheath. H.DIF showing IgG pemphigus-type deposits.

tests revealed elevated CEA level – 8.05 ng/ml (cut-off point 5 ng/ml) with normal levels of other cancer biomarkers (CA19-9, Ca125, AFP). She was treated with cyclophosphamide, doxycycline and high doses of both intravenous and oral steroids.

She was readmitted to the ward six months later with erosions on buccal mucosa, base of the mouth, soft palate and epiglottis. Laboratory tests revealed elevated CA19-9 level: 843.8 U/ml (cut-off point 37 U/ml). After achieving remission of lesions, she was directed to oncology outpatients to screen for malignancy.
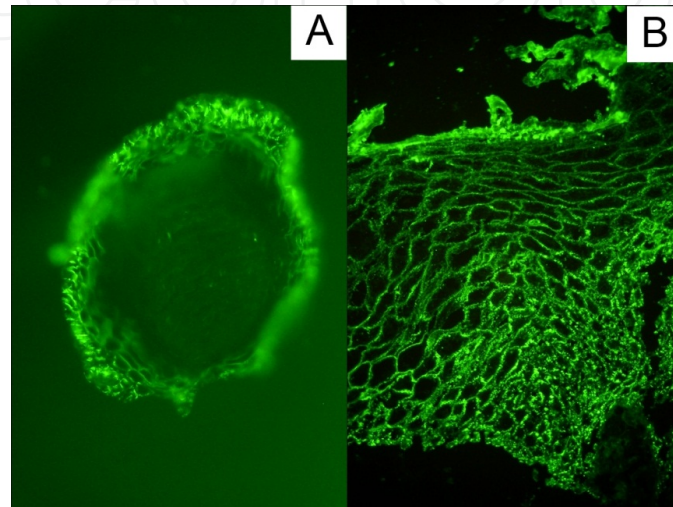
Figure 6. A. hDIF visualizing IgG1(++) deposits in the outer root sheath. B. DIF of perilesional mucosa revealing IgG1(++) deposits in intercellular spaces of lower layers of oral epithelium.

6.1.7. Case 7 — Pemphigus foliaceus / squamous cell carcinoma of external nose and upper lip

A middle-aged man with exophytic ulcerative nasal tumor was diagnosed with paranasal sinuses roentgenogram revealing massive shade of polycyclic outline. Surgical excision of the external nose tumor infiltrating upper lip was performed in oncology center (Fig. 7A). Exophytic lesion was described by a pathologist as carcinoma planoepitheliale keratodes (G2). The patient was frequently monitored in oncology outpatients finding no features of tumor recurrence.

Two years afterward, erythemous plaques with flaccid serous blisters, oozing erosions and crusts appeared on lower limbs. It took several weeks until lesions generalized and occupied trunk, limbs, head and intertriginous regions forming vast desquamative surfaces of flaky puff pastry-like appearance (Fig. 7B). Mucous membranes remained free of lesions. Due to ineffective ambulatory management, he was directed to dermatological ward with tentative diagnosis of PF.

Histological features of perilesional skin supported PF diagnosis. IIF on monkey esophagus revealed serum IgG pemphigus-type antibodies against desmosomal proteins of spinous layer of epidermis – titer 1/320, yet IIF on rat bladder epithelium as a substrate did not detected circulating PNP-type autoantibodies. DIF of perilesional skin visualized

well-defined IgG(+++) and IgG4(+++) deposits in intercellular spaces of lower layers of epidermis and linear C3(+) deposits alongside DEJ (Fig. 7C). Serum anti-DSG1 IgG ELISA was positive – level >150 AU/ml (cut-off point 41 AU/ml), whereas serum anti-DSG3 IgG ELISA proved negative – level 6.20 AU/ml (cut-off point 40 AU/ml). The molecular tests confirmed the PF diagnosis. He was treated with oral/intravenous steroids and cyclophosphamide, azathioprine and doxycycline as adjuvant treatment. The compliance in ambulatory care was poor as the patient repeatedly was treated in dermatological ward with IIF IgG pemphigus-type antibody titer reaching 1/2560.
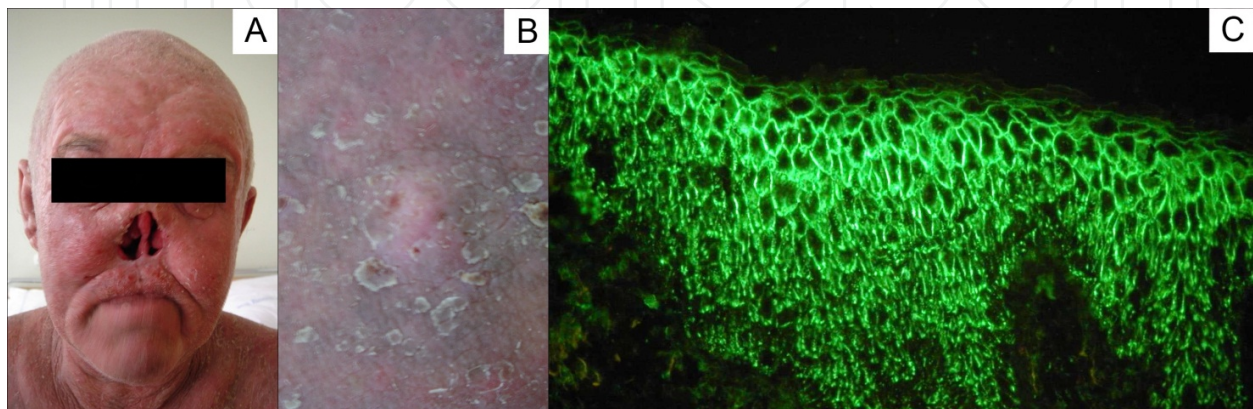
Figure 7. A. Nose stump after tumor excision. Courtesy of S. Stusek MD. B. Flaky puff pastry-like desquamative lesions on the trunk. Courtesy of S. Stusek MD. C. DIF of perilesional skin: intense pemphigus IgG4(+++) deposits.

6.2. Subepidermal autoimmune blistering diseases

6.2.1. Case 8 — Bullous pemphigoid / colon cancer

An elderly man was directed to chirurgical ward due to ileus. He underwent left hemicolectomy and forming of colostomy because of appendicitis, chronic peritonitis and colon cancer. Histopathological examination of the excised material revealed partially gelatinous tubular adenocarcinoma (G2; T4N0M0) infiltrating pericolic adipose tissue (Fig. 8B).

After the surgery, eczematous vesicular oozing eruption appeared on the surrounding of the stomy (Fig. 8A), while itchy well-tense bullae occurred on the skin of the back covering trunk and limbs in a few weeks. Histopathological and immunopathological tests were performed in dermatological outpatient ward two years after operation. Histology of the perilesional skin showed subepidermal vesicle filled with inflammatory cells with predominance of eosinoiphils (Fig. 8C). Perilesional skin DIF revealed linear deposits of IgG4(++) and C3(+++) along dermal-epidermal junction (DEJ) (Fig. 8D). IIF, performed on monkey esophagus as a substrate, was negative for IgG serum autoantibodies against desmosomal proteins of keratinocytes and basement membrane antigens. ELISA anti-BP180NC16a examination was positive for serum IgG antibodies against BP180 – titer 60.47 U/ml (cut-off point 9 U/ml), that enabled the diagnosis of trauma-induced and paraneoplastic BP at the molecular level. Control chest X-ray and ultrasonography of the abdomen did not showed neoplasm.

BP tend to manifest in natural and iatrogenic orifices featured by transient epithelium (e.g. the scar or the stomy site). It may be possible, that malignant tumor causing pathological immunization triggered the onset of this subepidermal dermatosis. The case is a hallmark of literature data [191–193].

### 6.2.2. Case 9 — Bullous pemphigoid / family history of renal cancer

A middle-aged female was directed to dermatological ward for diagnostics and treatment of disseminated itchy blisters and vesicles on erythematous skin (Fig. 9A, B) dating back two months. Her family history was significant for renal cancer coexisting with a subepidermal IgG-mediated bullous dermatosis, most likely BP, in grandmother. Her laboratory test were noncontributory. Immunohistochemical study showed subepidermal blister with neutrophil elastase (NE) deposits (Fig. 9C). IIF on monkey esophagus was positive for serum IgG pemphigoid-type antibody against DEJ proteins – titer 1/80. DIF of the perilesional skin revealed IgG1(+), IgG4(+) and C3(++) deposits along DEJ (Fig. 9D). Direct immunofluorescence test on salt-split skin (ssDIF) showed IgG4(+) and C3 deposits on epidermal side of the split. Aforementioned methods made it possible to diagnose BP and begin treatment with oral/ topical steroids, cyclophosphamide, doxycycline and antihistamines. Because of family history of autoimmune blistering dermatosis coexistent with cancer, the patient was advised to undergo meticulous follow-up to reveal any signs of malignancy as soon as possible.

6.2.3. Case 10 — Mucous membrane pemphigoid / hodgkin lymphoma

An elderly female, with swollen left supraclavicular lymph nodes, weight loss, fatigue, low grade fever and night sweats, was admitted to internal diseases ward for diagnostics. Both clinical symptoms, laboratory tests and histological examination of lymph node supported the diagnosis of Hodgkin lymphoma (IIB). She was treated with ABVD chemotherapy regimen (adriamycin, bleomycin, vinblastine, dacarbazine) and COPP regimen (cyclophosphamide, vincristin, procarbazine, prednisone) - due to bad tolerance of anthracyclines, achieving lymphoma remission.

Six years later, she called ENT professional due to dysphagia, oral itching and numerous painfull erosions on oral mucosa covered with whitish coating (Fig. 10A). The lesions were diagnosed mycologically as oral candidiasis (Candida famata, Candida glabrata). Antimycological treatment seemed ineffective and another erosive lesion (3 cm in diameter) appeared in umbilical region (Fig. 10B). She was directed to dermatological ward for further diagnostics and treatment six months later. Her medical history was also significant for total hysterectomy and episode of upper gastrointestinal bleeding (diffused intestinal metaplasia of the stomach mucosa; coagulated). Laboratory blood tests showed increased sedimentation rate and CRP. IIF on monkey esophagus did not revealed circulating IgG antibodies against desmosomal proteins of keratinocytes and basement membrane antigens (Fig. 10C). DIF of the perilesional skin from the umbilical region showed linear deposits of IgG(+/-), IgG1(+), and C3(+) along dermal-epidermal junction (Fig. 10D). In natural blister, autoantibody deposits were seen on epidermal side of the split. The diagnosis of MMP was based on clinical and DIF findings fulfilling the criteria of this dermatosis.
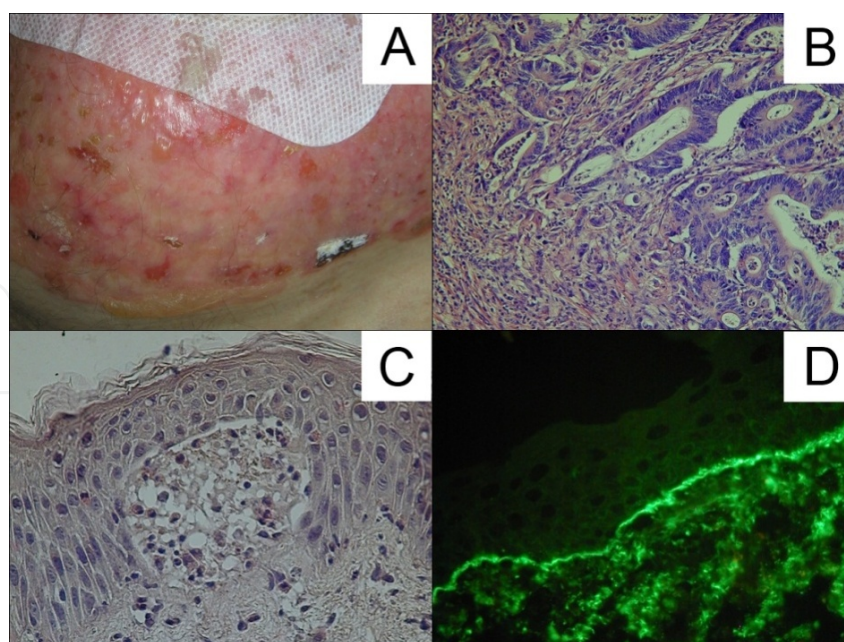
Figure 8. A. Blisters and their evolutionary lesions on inflamed skin around colostomy. B. A part of neoplastic infiltrate in the wall of large intestine showing cramped glandular ducts with irregular shapes. Epithelium cells with high-grade atypical cells. Inflammation of the periphery. H+E staining. Courtesy of I. Turczuk-Bierła MD. C. Histology of perilesional skin: Subepidermal vesicle with admixture of eosinophils within it. H+E staining. D. DIF of the blister skin margin: linear IgG4(++) deposits along DEJ.
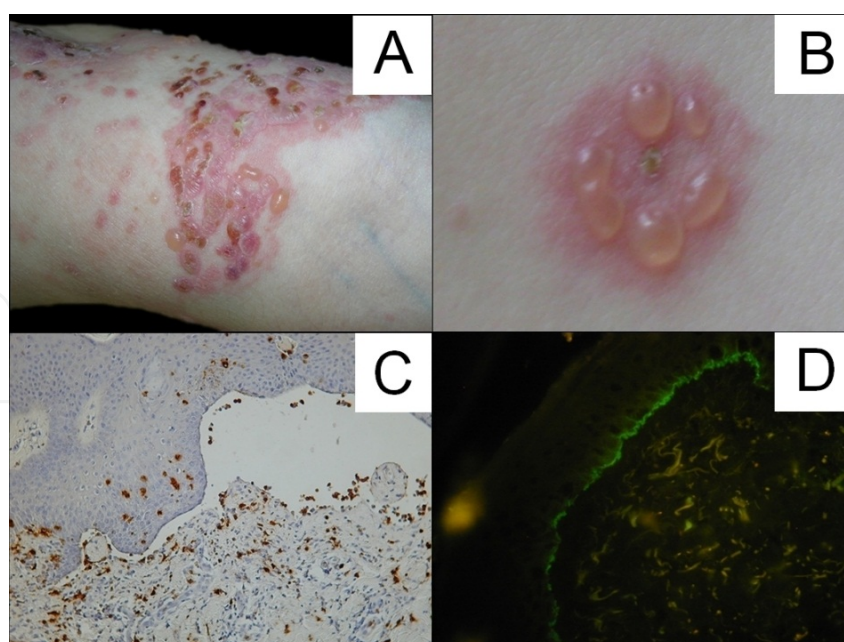
Figure 9. A. Erosions and bullae on erythematous skin forming "string of beans". B. Group of small blisters forming "cluster of jewels". C. Immunohistochemical study of the lesional skin. Visualization of neutrophil elastase (NE) deposits in the subepidermal blister. D. DIF on the perilesional skin: linear IgG4(+) deposits along DEJ.
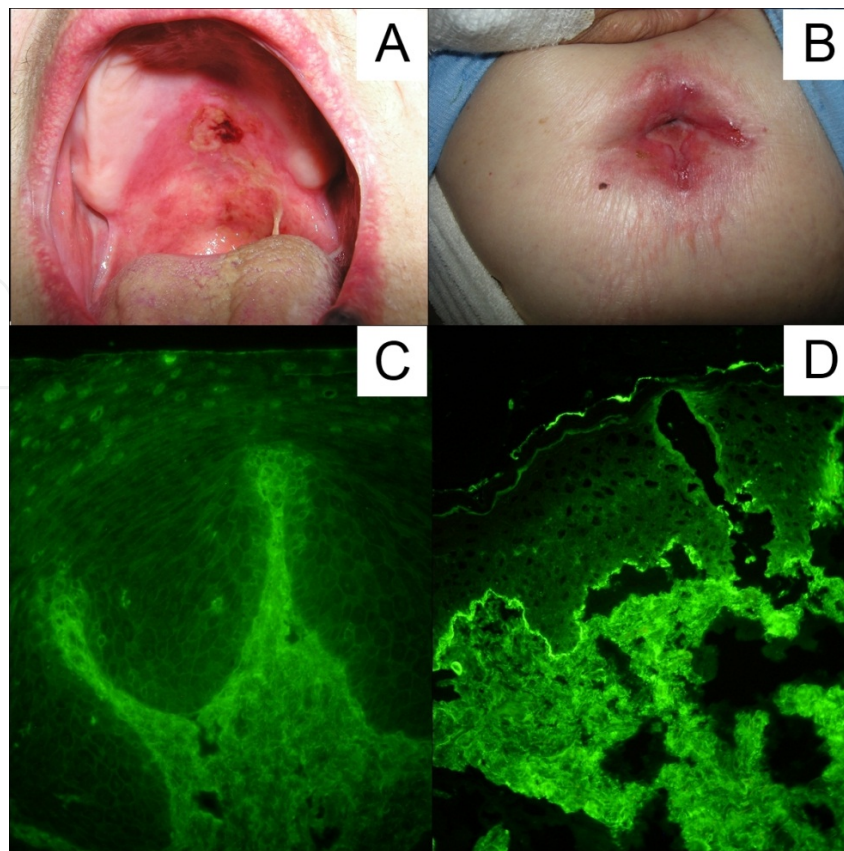
Figure 10. A. Mucosal erosions in oral cavity. B. Erosion in the navel. C. IIF study revealing no IgG antibodies binding either desmosomal proteins of keratinocytes or basement membrane antigens. D. DIF of the perilesional navel skin: linear IgG1(+) deposits alongside DEJ. Autoantibody deposits on epidermal side.

### 6.2.4. Case 11 — Bullous pemphigoid / renal cancer / prostate cancer

An elderly man visited the dermatologist due to disseminated erythematous itchy lesions, papules, erosions and a few well-tensed blisters filled with serous exudate on the forearms, arms and trunk (Fig. 11A, B). He was treated without clinical effect with antibiotics, antihistamine drugs and oral steroids. After a month, he was directed to dermatological ward for further diagnostics.

His medical history was significant for nephrectomy because of carcinoma clarocellulare, prostate adenocarcinoma (Gleason 1+3=4) treated with brachytherapy (HDR; 20 Gy) and radiotherapy, two hypermetabolic abdominal foci at level of kidney vessels in PET (supposedly metastatic lymph nodes), thyroid nodule and testis hydrocele. Laboratory tests revealed increased CRP levels, monocytosis, eosinocytosis, hypertriglyceridemia.

Histology of the perilesional skin showed subepidermal blistering and inflammatory mixed infiltrate with neutrophils and eosinophils (Fig. 11C). DIF of the perilesional skin of gluteal region showed linear deposits of IgG1(+), IgG4(++) and C3(+) along DEJ. DIF performed on vesicle margin skin showed linear deposits of IgG(+), IgG1(+), IgG4(+++) and C3(++) along dermal-epidermal junction. (Fig. 11D). IIF on monkey esophagus did not revealed

circulating IgG antibodies against desmosomal proteins of keratinocytes and basement membrane antigens. ELISA test revealed increased serum anti-BP230 IgG level – 81.356 RU/ml (cut-off point 20 RU/ml), yet circulating anti-BP180 IgG level was normal – 8.037 RU/ml (cut-off point 20 RU/ml). Vesicular and paraneoplastic BP was confirmed at the molecular level.
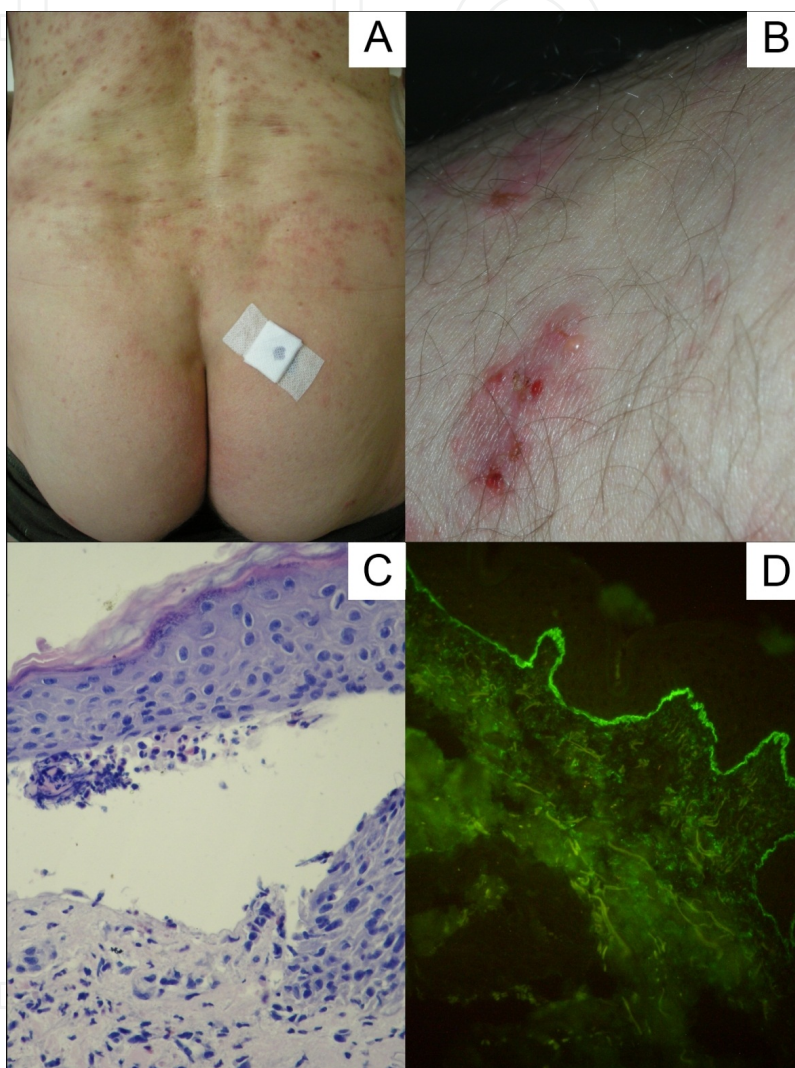

Published in [220].

Figure 11. A. Erythemous/oedematous lesions and erosions on the back in patient with vesiculous form of BP. Sticking plaster marks the site of biopsy. B. Vesicular lesions on posteriomedial surface of the left arm. C. Histology of subepidermal blister. Inflammatory mixed infiltrate with neutrophils and eosinophils. H+E staining. D. DIF on perilesional skin: IgG4 deposits along DEJ.

6.2.5. Case 12 — Bullous pemphigoid / lung cancer

A middle-aged heavy smoker visited dermatologist because of disseminated eruption of well-tensed painful blisters (Fig. 12A). Histological examination was suggestive of BP (Fig. 12B).

DIF of perilesional skin revealed linear deposits of IgG4(+) and C3(++) along dermal-epidermal junction (Fig. 12C). IIF on monkey esophagus did not revealed circulating IgG antibodies against either desmosomal proteins of keratinocytes or basement membrane antigens. The patient was directed to dermatological ward for further diagnostics. Laboratory tests showed leukocytosis, increased sedimentation rate and CRP. Apart of slightly increased CEA (6.79 ng/ml; cut-off for non-smokers 5.00 ng/ml, for smokers 6.50 ng/ml), other cancer biomarkers (AFP, CA19-9, Ca125, PSA) were negative. ELISA study was positive for serum anti-BP180 IgG – 19.50 RU/ml (cut-off point 9 RU/ml), yet negative for serum anti-BP230 IgG – 0.00 RU/ml (cut-off point 9 RU/ml). The diagnosis of BP was established. Abdominal ultrasound displayed enlarged liver without visible focal changes. Chest x-ray revealed a tumorous mass (7.0 cm x 6.6 cm), in middle lobe of the right lung, infiltrating lower root (Fig. 12D). Chest CT showed heterogeneous tumor of the right lung with consequent emphysema and metastatic mediastinal lymph nodes.

Consulting pulmonologist ordered further diagnostics and treatment in pulmonological ward, where bronchofiberoscopy was performed. With the histological diagnosis of carcinoma planoepitheliale akeratodes (G3; T4N2M0; IIIB) the patient began chemotherapy (cisplatin/vinorelbine regimen), yet he died within months.
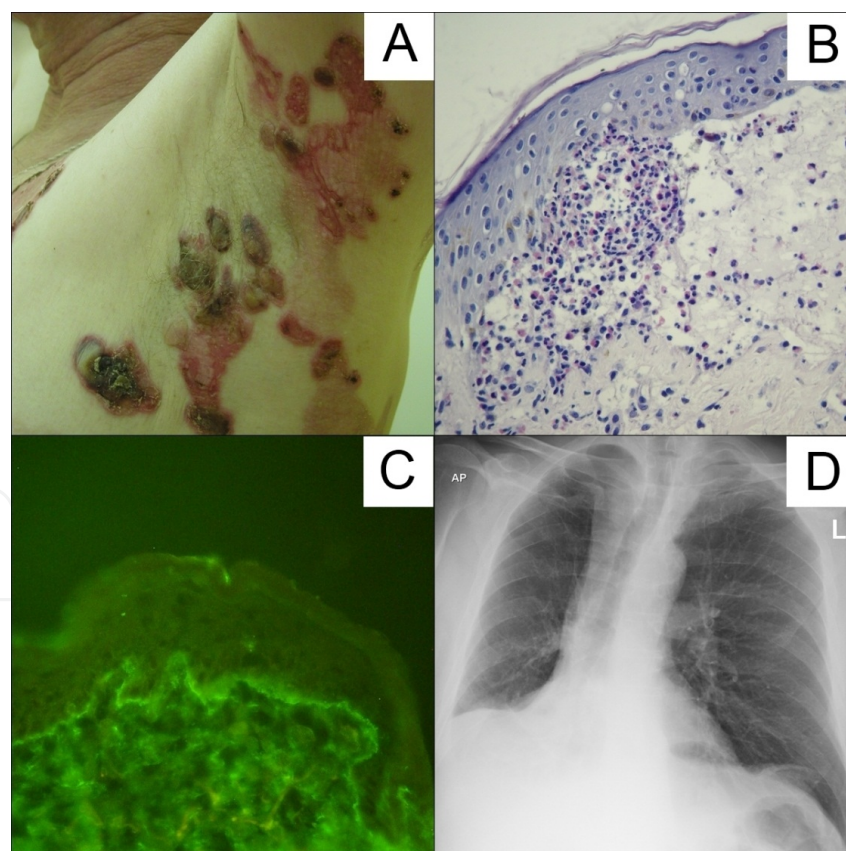
Figure 12. A. Painful well-tensed blisters, crusts and erosions on erythematous skin of the axillary area. B. Histology: subepidermal vesicle with abundant eosinophil infiltrate. H+E staining. C. DIF: linear deposits of IgG4 along DEJ. D. Chest x-ray: solid mass in middle lobe of the right lung, Tumor infiltration of lower lung root.

6.2.6. Case 13 — Bullous pemphigoid / prostate cancer

An elderly man consulted dermatology outpatient clinic due to itchy and painful well-tense blisters on the legs and subsequently on flexural surfaces of the forearms dating back four months (Fig. 13A). Perilesional skin bioptate and patient's blood sample were obtained for diagnostic purposes. Histology showed subepidermal blister. Major basic protein was visualized with immunohistochemical method marking eosinophil infiltrate (Fig. 13B). DIF study revealed linear deposits of IgG1(+), IgG4(+) and C3(++) along DEJ (Fig. 13C). IIF on monkey esophagus revealed circulating pemphigoid-type IgG, IgG1 and IgG4 antibodies against basement membrane antigens, of titers respectively 1/320, 1/160 and 1/160 (Fig. 13D). He was treated with limecycline, antihistamine drugs and incidental intramuscular steroids and was directed to dermatological ward, with tentative diagnosis of BP, for further diagnostics and treatment.

On admission he presented oozing erosions and well-tensed blisters filled with serosanguineous exudate on the right forearm. His medical history was significant for prostatic cancer (treated for 8-year-period with hormonal therapy) and orchidectomy. He was treated by urologist with tamsulosin, cyproterone, finasteride, flutamide, leuprorelin and goserelin. Several months before lesions' appearance, the urologist ceased the hormonal treatment, finding it purposeless. Laboratory tests revealed erythrocytopenia, increased sedimentation rate and PSA (17.49 ng/ml; cut-off 4.00). Other cancer biomarkers (CEA, AFP), FOBT and stool examination for parasite infestation were negative. ELISA test performed on patient's serum and blister fluid showed increased anti-BP180 IgG level: 14.01 RU/ml and 13.21 RU/ml respectively (cut-off 9 RU/ml) and increased anti-BP230 IgG level: 90.66 RU/ml and 75.85 RU/ml respectively. The diagnosis of BP as a paraneoplastic syndrome was made. Due to previous oncologic history, patient was urgently directed to urologist. Leuproreline readministration with immunosuppressive and anti-inflammatory treatment enabled remission of cutaneous lesions.

6.2.7. Case 14 — Ocular mucous membrane pemphigoid / endometrial cancer

A middle-aged woman was admitted to dermatological dispensary due to erosive lesions on oral mucosa lasting for 2 years. She was treated by stomatologist, but without effect. Moreover, due to involvement of conjunctivae two months earlier, she called the ophthalmologist, yet the administered treatment seemed insufficient.

She was directed to dermatological ward for diagnostics. Her medical history was significant for hysterectomy and adnexotomy with fistula and colon partial resection and transversostomy due to endometrial adenocarcinoma infiltrating colon, causing recto-vaginal fistula (G2; pT3aNx). She was planned for chemotherapy by gynaeco-oncologist. Her laboratory tests showed increased sedimentation rate and increased antinuclear antibodies (ANA) titer. IIF on monkey esophagus was negative for serum IgG autoantibodies against both desmosomal proteins of keratinocyte and basement membrane antigens. DIF on oral mucous membrane bioptate revealed scant linear C3 deposits along DEJ. Both clinical and immunopathological findings supported the diagnosis of ocular MMP.
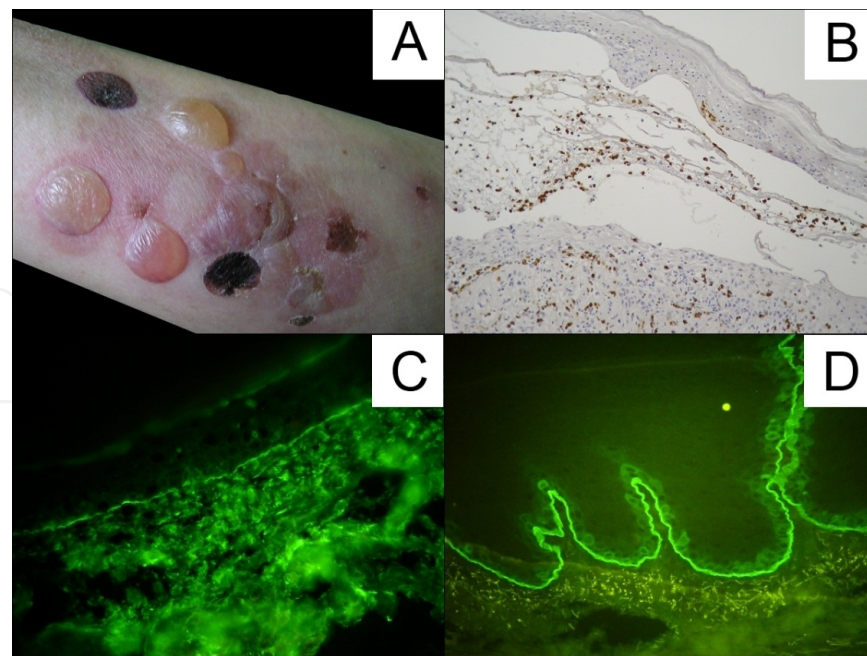
Figure 13. A. Blisters and their evolutionary lesions on urticarial skin on the flexural surface of a forearm. B. Eosinophil major basic protein (MBP) deposits in lesional skin. Immunohistochemistry of subepidermal blister showing histological features of regeneration. C. DIF of perilesional skin: linear IgG1(+) deposits along DEJ. D. IIF on monkey esophagus: IgG4 antibodies against epithelial basement membrane antigens.

6.2.8. Case 15 — Bullous pemphigoid / breast cancer

An elderly female with itchy bullous eruption on acral parts of the limbs visited the dermatological outpatient clinic. The lesions dated back four months and suggested BP. Her medical history was significant for mastectomy due to breast cancer (infiltrating desmoplastic ductal and intraductal carcinoma of intermediate grade of malignancy; G2 according to Bloom-Richardson Grading System). DIF study of the perilesional skin sample revealed linear IgG4(+/-) and C3(++) deposits along DEJ. IIF, on monkey esophagus as a substrate, revealed neither serum IgG nor IgG4 antibodies against desmosomal proteins of keratinocytes and basement membrane antigens. ELISA study defined serum anti-BP180 IgG level as >200 RU/ml (cut-off point 20 RU/ml), yet serum anti-BP230 IgG level was normal – 3.182 RU/ml (cut-off point 20 RU/ml). With molecular methods, the tentative clinical diagnosis of BP was confirmed. The patient remained in control of both dermatology and oncology outpatient clinics.

6.3. Discussion on MAABD cases

ABD can insidiously don the masks of other diseases imitating e.g. ulcerative carcinomas, paronychia, eczema or pruritus. Generalized or localized, the eruption may remain disguised for many months and years until the diagnosis is reached. In the light of contemporary data, ABD circle shift in one patient by acquiring autoimmunity to new epitopes (via epitope spreading or bystander effect) is possible. It should be concluded, that every circle is not a coherent group of diseases, yet forms a continuum of autoimmune blistering dermatoses within autoimmune

multiorgan syndrome. The causative relation between ABD and cancer is difficult to establish, as both malignancy and ABD develops and stay undiagnosed over some time period.

In review based on PubMed, Scopus and EMBASE literature data, SCC has been found responsible of projection the majority of paraneoplastic syndromes, with pemphigus being one of the commonest dermatological conditions among them [194]. Case 1 and 2 both presented carcinoma planoepitheliale/SCC with PV. The latter entity, by imitating mucosal neoplastic process, presumably confused the clinicist and elongated the onset-diagnosis period. Interestingly, both cases showed recrudescence of their pemphigus lesions after radiotherapy. It seems to be a common finding in ABD, thus supports the role of radiotrauma-induced denudation of formerly hidden epitopes in disease pathogenesis. The issue of SCC driving autoimmunity is still enigmatic, yet change in DSG profile promoting tumor cell migration may play a role in autoaggresion [177]. Similar cases to abovementioned ones were reported in literature [17,195]. As pseudomyxoma peritonei classification still causes contro-versy [196], the association between PF and ovarian/appendiceal tumor in case 3 is disputable. Some researchers speculated on the role of HPV16 and bacteria in development of this tumor of appendiceal origin [197,198]. A single case of PNP, breast tumor and pseudomyxoma peritonei was mentioned in literature [53]. To our best knowledge, case 3 is the first report on coexistence of these two conditions. The concomitance of exophytic thoracic SCC-tumor and PF (case 4) seem to be well-defined, yet behavior of the patient is difficult to comprehend since his stinky tumor was present for years. Apparently, his PF lesions finally prompted him to seek dermatological advise, but not the tumor itself. Apart of that, the case 5 is no less enigmatic. PV may imitate multiple conditions and it should be noted, that his lip lesion (described correctly as SCC by general pathologist) coexisted at the same site with the lesion of PV initially missed by general pathologist but diagnosed as such by cutaneous pathologist by reevaluation of initial specimen. Both above cases are portrayal of suspicious association of SCC preceding pemphigus, whereas case 5 features additionally shifting PV phenotype, supposedly because of active long-term pathological autoimmunization syndrome involving epitope spreading phenomenon. Case 5 was mentioned in literature [190]. CA19-9 marker is tumor-associated, but not tumor-specific marker. It is used as a screening test for gastrointes-tinal adenocarcinomas (colorectal, hepatic, lung, ovarian carcinoma and few non-malignant conditions), first of all for pancreatic cancer [199]. Association of PV with breast cancer (case 6) or potential gastrointestinal tract adenocarcinoma is disputable. The case may be considered a model for post-cancer ABD eruption and stands as an evidence for strong need of regular screening for malignancy in ABD patients. As far as case 7 is concerned, once again we find it questionable whether excised nasal/labial tumor was assessed properly as a cancerous or was it just a limited exophytic lesion heralding PF – chancre of pemphigus [200]. There is limited data concerning SCC, second commonest skin cancer coexistent with PF [201]. The negative correlation between DSG1 expression and degree of dysplasia in SCC is an interesting issue indicating contribution of desmosomal adhesion glycoproteins in cancerogenesis [202].

BP tends to manifest in natural and iatrogenic orifices featured by transient epithelium (e.g. iatrogenic – the scar or the stomy site) (case 8). It seems coherent that malignant tumor causing pathological immunization triggered the onset of BP. It was suggested that BP may be

secondary to surgical procedures exposing sequestered antigens of colon mucosa (particularly BP180) [185,203–206]. The case is a hallmark of literature data [191–193]. As pemphigus and pemphigoid may occur as a paraneoplastic syndrome accompanying malignant tumor, it might be reasonable to form an online national registry of patients with ABD. Case 9 was included to visualize that need. Although both ABD may not contain "paraneoplastic" attribute, it is highly advisable to monitor all the patients with all ABD as group of high risk of developing malignancy [16]. There is scant data on coexistence of MMP and Hodgkin lymphoma (case 10) [207,208]. Moreover, the association between pemphigoid and non-Hodgkin lymphoma may seem to be better exemplified [19,209,210]. Nonetheless, each malignant lymphoproliferation may lead to impairment of immunological mechanisms via the change of antigen suit, cytokine production, distorted antibody production and abnormal cytokine production affecting many molecular pathways, both known and unknown. As far as case 11 is concerned, practising dermatologist, perhaps suspecting Cottini form of DH, obtained skin sample for DIF from lesion-free gluteal region (Fig. 11A). However, that area should be regarded as non-optimal for diagnosing that form of DH with DIF [211]. Luckily, BP-indicative deposits of immunoreactants were present at both lesion-free and perilesional sites. The link between malignancy and pemphigoid in case 11 may be multi-sided. Both renal and prostate cancer might be suspicious of contribution to autoaggression [23,67,71,180,212,213] and the role of radiotherapy should not be considered irrelevant. Renal cancer elicits paraneoplastic syndromes in 40% of patients, although dermatological manifestations seem to be extremely rare [70]. Cancerous lung involvement in BP (as in case 12) was previously reported [34], yet pulmonary cancer seems to be more PV-associated. The cessation of hormonal treatment seemed to trigger BP as a symptom of recurrence of prostate malignancy (case 13) [21]. BP and prostate adenocarcinoma might be interrelated by BP180 issue. It was observed, that prostatic malignant tumors may lack of hemidesmosomal structures – BP180 and less commonly BP230 [180]. Abnormal composition of detectable basement membrane antigens participating in multiple molecular pathways may disbalance mechanisms of self-tolerance consequently stimulating the pathological autoimmunity. Induction of pemphigoid by trauma (in case 14 – by hysterectomy with partial colon resection), as reported in literature [214], may seem a reasonable explanation. There is one similar report on anti-laminin-332 MMP presumably associated with endometrial carcinoma [215]. BP in case 15 may be regarded secondary to breast cancer. It may be possible, that the distortion of cell cohesion in neoplastic cells leads to exposing normally hidden antigens or new epitopes are recognized by the immunocompetent cells. There are reports mentioning overlapped breast cancer and BP [20,84] as well as reports describing the evoking of autoimmune blistering dermatosis after breast radiotherapy [216–218], that may change antigenicity of the malignant cells.

Cancer research gives molecular evidence for tumor genetic instability. Vast array of unique tumor-specific neoantigens are presented on tumor's MHC molecules. Their recognition by T-cells could induce anti-tumor immunity [219]. Antibody-assisted defense against tumor may explain the fact of spontaneous cancer remissions. The other side of the coin may be the autoimmunity caused by unspecific tumor antigens, that are displayed in many tissues being easily accessible for T-cells. Hypothetically, some ABD might be really MAABD with tumor eradicated in early phase.

7. Conclusion

The diversity of ABD results from diversity of recognizable epitopes of adhesive, desmosomal, hemidesmosomal and basement membrane antigens that interact playing complicated role in securing tissue integrity, intercellular communication and skin growth. Aberrant adhesive molecule expression via epitope spreading, bystander effect and various signaling pathways, may contribute to increased risk of developing cancer and its further prognosis. The altered expression of adhesion complex molecules is thought to be vital for carcinoma motility and invasion. The conjunction of malignancy and ABD phenomenon still remains an area of interest of researchers worldwide, as it may benefit in development of more specific diagnostic tests and precise therapeutic strategies.

Concomitance of malignancy and these serious clinical conditions may dramatically decrease the patient survivorship. The wise clinician ought to trace potential malignancy in each and every one of the patients with ABD, regardless of deceptive lack of "paraneoplastic" epithet in the currently used misleading nosology for majority of those dermatoses, as such an association between those two groups of entities, was demonstrated not to be rare. Therefore, the diagnosis of ABD should be followed not only by screening, but also monitoring/periodical checking for malignancies. Moreover, the replacement of indiscriminate immunosuppressive therapy by individualized targeted therapy should be recommended. There is burning need for awareness of such coexistence also among oncologic patients, as ADB may herald the recurrence of malignancy.

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We dedicate this work to our patients suffering from malignancy concomitant with autoimmune blistering dermatosis

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