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Paraneoplastic pemphigus and reported, identified underlying diseases

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Abstract:

Introduction: Pemphigus is a rare group of autoimmune diseases that promote development of various skin eruptions, the most commonly it presents with blisters. The several types of pemphigus are: pemphigus vulgaris, pemphigus foliaceus, intraepidermal neutrophillic IgA dermatosis and especially rare type- paraneoplastic pemphigus, which is main topic of this publication. Paraneoplastic pemphigus is a disease which affects patients with developing carcinogenesis process. Usually it is a malignant process, but there are also some cases which describe paraneoplastic pemphigus associated with benign tumors. Because of its occurence our current level of knowledge about different aspects of paraneoplastic pemphigus is not final and as comprehensive as researchers and patients wish.

Aim of study: The main purpose of this publication is presentation a review of literature about paraneoplastic pemphigus- its epidemiology, physiopathology, pathomorfology, clinical features,

and description of different types of benign or malignant processes which concomitence with paraneoplastic pemphigus.

State of knowledge: Paraneoplastic pemphigus is a rare autoimmune disease, which aspects are not widely described, but there are some reports about epidemiology, pathophysiology, histopathology, treatment and associated confirmed malignancies. The challenge for future is to formulate clear, formal, treatment protocols for paraneoplastic pemphigus.

Conclusion: Paraneoplastic pemphigus is a very fascinating disease for researchers because there are still very limited reports and statistics about this very rare disorder. Nonetheless year by year our level of knowledge about pathogenesis, clinical features, associated malignant and benign processes is growing and it can affect more personalized, effective treatment methods and protocoles.

Keywords: paraneoplastic pemphigus, dermatology, oncology, cancer

Paraneoplastic pemphigus- epidemiology

Epidemiology reports are underreported and are not enough to be precise in calculations. Lamia Jelti and co-authors defined the epidemiology of paraneoplastic pemphigus as 5% of all pemphigus cases. They point that annual incidence rate per million inhabitance in France of all pemphigus types, not only paraneoplastic pemphigus is 1.5 per million. This example demonstrates very well how rare and unique is this pemphigus variant. (1)

Paraneoplastic pemphigus- pathogenesis

A. Ohzono and co-authors focused on clinical and immunological findings in 104 cases of paraneoplastic pemphigus (2). They point and accentuate that although there are many reports of

sporadic patients with paraneoplastic pemphigus, only a few systematic studies on large cohorts of patients have been reported. The most common neoplasms in this cohort included malignant lymphomas, malignant solid tumors and Castleman disease. Novel ELISAs for desmocollins (Dscs) showed that 19 (18.6%), 42 (41.2%) and 62 (60.8%) of 102 patients with PNP showed antibodies to Dsc1, Dsc2 and Dsc3, respectively. Thirty-two (60%) of 53 patients had antibodies to alpha-2-macroglobulin-like protein 1 (A2ML1). The conclusion is that desmocollins and also A2ML1 should be considerated as possible elements which can be useful as paraneoplastic pemphigus diagnostic tool. D Mimouni and co-authors analysed the clinical and immunopathological features of paraneoplastic pemphigus, but only in pediatric population included (3). 14 patients under the age of 18 years with a confirmed diagnosis of paraneoplastic pemphigus were analysed by various immunological tools and techniques- for example immunofluorescence, immunoprecipitation for plakin antibodies or ELISA for detection of desmoglein 1 and desmoglein 3 autoantibodies. Indirect IF detected IgG antibodies were detected in all cases, immunoprecipitation revealed IgG autoantibodies against desmoplakin I, envoplakin and periplakin in all cases, and against desmoplakin II and the 170-kDa antigen in 13 and 10 patients, Dsg3 and Dsg1 autoantibodies were present in 10 and 3 patients, respectively, and plectin autoantibodies in 13 patients.

Paraneoplastic pemphigus- clinical features and diagnosis

A variety and range of potential lesions and its morphologies is very wide. Clinical features may include- typically very itchy polymorphic skin lesions seen after mucous membrane involvement, blisters, haemorrhagic crusting, ulceration involving especially oropharynx or nasopharynx, lichenoid eruptions which is characterized by damage and infiltration between the epidermis and dermis. Typical is transformation of described symptoms from one form to another. There are distinguished five main type of clinical presantion of paraneoplastic pemphigus. Pemphigus-like, pemphigoid-like, erythema multiforme-like, graft-versus-host disease like, lichen planus-like (4,5,6). Pemphigus-like is characterized mainly by superficial vesicles, flaccid blisters, crusted erosions. Fundamental clinical presentation of pemphigoid-like are scaling erythematous papules and tense blisters, for erythema multiforme-like: scaling erythematous papules and severe, polymorphic cutaneous or mucosal lesions, for Graft- versus- Host disease- diffuse red, scaly, dusky papules and for lichen planus- like- small red to violaceous flat-topped scaly papules. In A.Ohzono and co-authors study an erythema multiforme-like presentation was most common (56%), pemphigus- like (41%), lichen planus- like (13%), pemphigoid- like (3%) (2).

Life-threatining complication which is postulated as associated with paraneoplastic pemphigus is restrictive bronchiolitis consistent with bronchiolitis obliterans. Can Chen and co-authors in 2023 described lung as the most frequent organ involved in paraneoplastic pemphigus and its frequency is estimated as 59.2% to 92.8% of paraneoplastic pemphigus cases (7). It is not a precise estamation, but as it was mentioned with regard to general epidemiology of this disease, reviews are still limited. Can Chen and co- authors in the same publication describe a first case of successful using of ibrutinib in treating paraneoplastic pemphigus related bronchiolitis obliterans concurrent with CLL. Also Kodai Kuriyama and co-authors described successful treatment of paraneoplastic pemphigus and bronchiolitis obliterans associated with follicular lymphoma with obinutuzumab and bendamustine (8). It can be a promising prognosis for future methods and algorithms of treatment.

In 2021 Steven Slovoda and co-authors presented a postulated diagnostic criteria based on literature analysis (9). The revised criteria, they postulate, include three major criteria and two minor criteria, whereby meeting either all three major criteria or two major and both minor criteria would fulfill a diagnosis of paraneoplastic pemphigus. The major criteria include- mucous membrane lesions with or without cutaneous involvement, concomitant internal neoplasm and serologic evidence of anti-plakin antibodies. The minor criteria include acantholysis and/or lichenoid interface dermatitits on histopathology and direct immunofluorescence staining showing intercellular and/or basement membrane staining. Of course the key to diagnosis and proper selection of treatment which can alleviate symptoms is looking for carcinogenesis process which concomitance with paraneoplastic pemphigus. Next part of this publication will include a description and literature review of different types of disorders which lead to development of paraneoplastic pemphigus.

Paraneoplastic pemphigus and reported, identified underlying diseases- frequency of associated neoplasms

Although there is limited amount of data, Ilana Kaplan and co-authors tried to pinpoint frequency of neoplasms associated with paraneoplastic pemphigus (10). Their review included 163 cases of paraneoplastic pemphigus reported between 1990 and 2003. Hematologic-related neoplasms or disorders were associated with 84% of the cases, with non-Hodgkin lymphoma (38.6%) as the most frequent, followed by chronic lymphocytic leukemia (18.4%) and Castleman's disease (18.4%). The

non-hematologic neoplasms comprised 16% of all cases: epithelial origin-carcinoma (8.6%), mesenchymal origin-sarcoma (6.2%), and malignant melanoma (0.6%). Carcinoma cases comprised 58% of the non-hematologic neoplasms. Carcinoma cases (n = 14) consisted of adenocarcinoma (n = 7), squamous cell carcinoma (n = 2), multiple skin tumors probably basal cell carcinoma (n = 1), and bronchogenic carcinoma (n = 1). Of the 10 (6.2%) sarcoma cases, there was one case each of leiomyosarcoma, liposarcoma, malignant nerve sheath tumor, poorly differentiated sarcoma, reticulum cell sarcoma, dendritic cell sarcoma and inflammatory myofibroblastic tumor.

Paraneoplastic pemphigus and non-Hodgkin lymphoma

Non- Hodgkin lymphoma is a group of blood cancers that includes all types of lymphomas except Hodgkin lymphoma. There are some factors which are exhibited and defined as promoters, initiators or catalysts of Non- Hodgkin development- Epstein-Barr virus, HIV, Hepatitis C, HHV-8, Helicobacter Pylori, some chemicals, radiation therapy or chemiotherapy or autoimmune diseases. The traditional and most often applicated treatment of Non-Hodgkin lymphoma includes chemotherapy, radiotherapy and stem-cells transplants. The most common chemotherapy is R-CHOP protocole- cyclophosphamide, doxorubicin, vincristine and prednizone + rituximab. (11)

Van der Waal and co-authors presented a case of paraneoplastic pemphigus as the manifestated symptom of a Non-Hodgkin lymphoma of the tongue (12). What is especially interesting about diagnostic path- although the various laboratory studies pointed to the diagnosis of paraneoplastic pemphigus, the underlying neoplasm was not detected until 6 months later.

Can Baykal and co-authors published a literature review on the association between paraneoplastic pemphigus and heamotological malignancies revealed a further history of rituximab use (13). There were included two patients with Non-Hodgkin lymphoma- 69 years female and 72 years male. Duration between malignancy and occurence of paraneoplastic pemphigus were 1 year for female and 11 years for male. It is valuable example how wide can be range of time between maligancy and paraneoplastic pemphigus development.

Paraneoplastic pemphigus and chronic lymphocytic leukemia

Chronic lymphocytic leukemia is a type of cancer which manifestates with excessive bone marrow lymphocytic production. Clinical stage of chronic lymphocytic leukemia is described according to

Rai and Binet classifications. Rai classification includes IV stages: stage 0 is only lymphocytosis, stage I is additionally associated with lymphadenopathy, stage II additionally- spleen/liver enlarged, stage III- Hb<11, stage IV- platelets < 100 000. Binet classification includes A, B and C stage. A- < 3 lymphoid areas enlarged, B- > 3 lymphoid areas enlarged. C- additionally Hb< 10 and platelets < 100 000. CLL is treated by chemotherapy, radiation therapy, biological therapy, bone marrow transplantation. (14)

Lei Cao and co-authors retrospectively reported six chronic lymphocytic leukemia with paraneoplastic pemphigus and the median time between the initial of chronic lymphocytic leukemia to paraneoplastic pemphigus was 36 months and the median survival rate from the moment of paraneoplastic pemphigus diagnosis was 26 months. They also present used therapeutical strategy- five patients were treated with combined regimens including rituximab, methylprednisolone, immunoglobulin, fresh frozen plasma and the last received ibrutinib combined with short-term prednisone. (15)

Paraneoplastic pemphigus and Castleman disease

Castleman disease describes a group of rare lymphoproliferative disorders (16). For this disorder typical are single enlarge lymph node or multiple enlarge lymph nodes located in different regions of body. Pathological features are increased number of follicles with large hyperplastic germinal centers and sheetlike plasmacytosis, regressed germinal centers, follicular dendritic cell prominence or dysplasia. There are some reports which describe paraneoplastic pemphigus and Castleman disease which concomitence. According to statistics mentioned above- Castleman disease is third the most frequent neoplasm among patients with paraneoplastic pemphigus.

Mariangela Irrera and co-authors presented a case of a 13 years old girl with a challenging diagnosis of paraneoplastic pemphigus and Castleman disease (17). They point, reviewing literature, that till 2023- 20 clinical cases of this association have been described in pediatric age. Unfortunately, because of challenging diagnosis and sporadic occurence- a range of diagnosis was from 3 weeks to 2 years.

Kelly K Barry and co-authors presented a multicenter case series of paraneoplastic pemphigus associated with Castleman disease (18). Two children, two adolescents and one young adult were included. Castleman tumors were located in retroperitoneum- 4 cases and axilla- 1 case. Three

patients had bronchiolitis obliterans, three had complete resection of their Castleman disease, two had partial resection. Three patients remained alive with a follow-up of 13 months.

Paraneoplastic pemphigus- different, reported, identified underlying neoplasms

Non-Hodgkin lymphoma, chronic lymphocytic leukemia and Castleman disease, which are described above, are three the most frequent reported in literature neoplasms associated with paraneoplastic pemphigus, but as mentioned statistics indicate, there are also other, more non-typical reported, indentified underlying neoplasms.

For example Hajar Moata and co-authors reported paraneoplastic pemphigus associated with prostate adenocarcinoma, they point that paraneoplastic pemphigus with solid cancer is extremely rare, in this case 69 year old patient presented spectacular response immediately after hormonotherapy with conventional immunosupressive drugs (19).

There are also unique and single reports which describe paraneoplastic pemphigus with follicular dendritic cell sarcoma, Waldenström's macroglobulinaemia, oral presentation of paraneoplastic pemphigus as the first sign of tonsillar HPV associated squamous cell carcinoma, renal cell carcinoma-induced paraneoplastic pemphigus, paraneoplastic pemphigus secondary to neuroendocrine carcinoma, paraneoplastic pemphigus associated with a pericardial ectopic thymoma (20,21,22,23,24,25,26,27,28,29,30,31).

Summary

Paraneoplastic pemphigus is a very fascinating disease for researchers because there are still very limited reports and statistics about this very rare disorder. Nonetheless year by year our level of knowledge about pathogenesis, clinical features, associated malignant and benign processes is growing and it can affect more personalized, effective treatment methods and protocoles. It is necessary to focus on next, new reports about different aspects of paraneoplastic pemphigus, update our epidemiological, diagnostic criteria and follow concrete, specific reports about paraneoplastic pemphigus and reported, identified underlying diseases.

Disclosures

Author's contribution:

Conceptualization- Paweł Iwańczuk

Formal analysis- Paweł Iwańczuk

Investigation- Paweł Iwańczuk

Writing- rough preparation- Paweł Iwańczuk

Writing- review and editing- Paweł Iwańczuk

Visualization- Paweł Iwańczuk

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