

# Pemphigus foliaceus in an elderly woman: advantages and limitations of histopathology in pemphigus

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## ABSTRACT

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**Introduction:** Diagnosing autoimmune blistering diseases is based on clinical presentation and direct immunofluorescence detection of circulating autoantibodies. However, a histopathological examination of the affected tissues may also be helpful in such a diagnosis.

**Objective:** To present a case illustrating that a histopathological examination facilitates the diagnosis of autoimmune blistering diseases, particularly for a patient with concomitant dermatological conditions.

**Case report:** We present the case of a 91-year-old female patient with symptoms of generalized scaly, crusted erosions on an erythematous base, who was diagnosed with psoriasis 10 years earlier. Based on a histopathological examination, there was a suspicion of pemphigus foliaceus, which was later confirmed by direct immunofluorescence and the multiparametric ELISA.

**Conclusions:** A histopathological examination is not obligatory for a pemphigus diagnosis; however, in ambiguous cases, where a patient has other concomitant dermatoses, it may significantly improve the accuracy of the diagnosis. The limitations and advantages of histopathological examinations in pemphigus are discussed.

**Key words:** histopathological examination, pemphigus foliaceus, autoimmune blistering diseases.

## INTRODUCTION

Pemphigus is a group of rare, chronic, and potentially life-threatening autoimmune blistering diseases (AIBD) of the skin and/or mucous membranes [1, 2]. Pemphigus foliaceus (PF) is characterized by the presence of circulating IgG antibodies targeting desmoglein 1 (DSG1), causing loss of adhesion between epidermal cells. This leads to acantholysis and the formation of bullous lesions and erosions. The diagnosis of pemphigus is based on clinical presentation as well as direct immunofluorescence (DIF)

and serum tests for circulating autoantibodies. A histopathological examination (HPE) of skin lesions, routinely stained with haematoxylin and eosin (H + E), although unable to detect crucial pathologic autoimmune phenomena, may reveal features suggestive of pemphigus, especially when assessed by an experienced dermatopathologist [3]. Due to the limited repertoire of microscopic patterns available for inflammatory dermatoses, a close, mutual collaboration between the clinician and the pathologist is required in order to make a precise diagnosis. Hence the concept of an international dermatopathological special-

ization, combining clinical and pathological issues. As far as the diagnosis of pemphigus is concerned, this examination does not make it possible to detect autoimmunity, the cardinal feature of these conditions. Acantholysis is not specific only to pemphigus group diseases, as it may also constitute an incidental finding in dermatitis herpetiformis. Apart from the pemphigus group diseases, acantholytic cells can also be present in Darier's disease, Hailey-Hailey disease, Grover's disease, acantholytic dermatosis localized to the vulvocrural area, linear epidermal nevus, warty dyskeratoma, acantholytic acanthoma, oral focal acantholytic dyskeratosis, carcinoma spinocellulare dyskeratoticum segregans, acantholytic variant of senile keratosis, and acantholytic dyskeratotic papules [4].

Our experience suggests that, in the diagnosis of a pemphigus group disease, due to cost-effectiveness, a three-component diagnostic approach is appropriate. This entails a clinical evaluation, a DIF (also for identification of IgG4 deposits), and serum biochemical/molecular tests, ideally using a multiplex approach, for the detection of autoimmune targets. However, the role of HPE is sometimes pivotal when the clinician fails to realize that they are dealing with a pemphigus group disease. Then, a properly interpreted HPE may provide clues as to the need for an

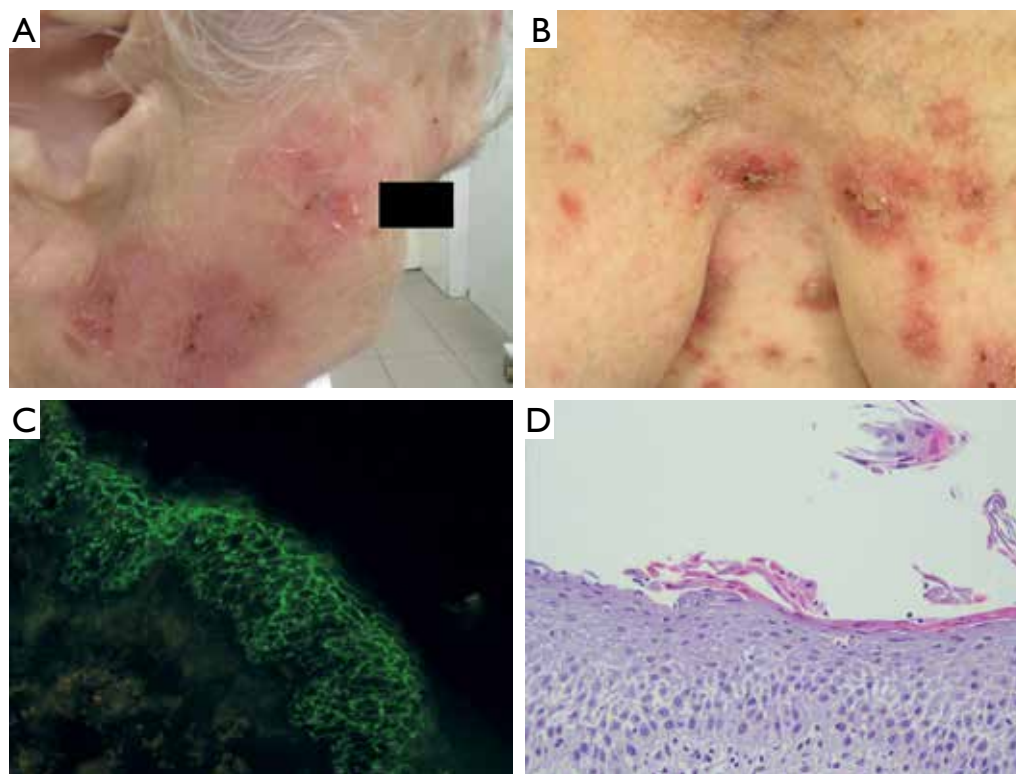
immunopathology examination, or it may suggest a differential diagnosis. However, this examination can be difficult to interpret unequivocally, because the lesions, whether untreated or inadequately treated before the laboratory diagnosis is made, are subject to temporal and spatial evolution; hence, the role of the specialist dermatopathologist cannot be overestimated. HPE may not show the obvious features of pemphigus. HPE is required in many clinical trials to qualify patients for these examinations. However, in our opinion, in case of AIBD, it should be optional rather than obligatory.

## OBJECTIVE

In this report, we discuss a significant case from our own clinical-laboratory research practice.

## CASE REPORT

A 91-year-old woman was admitted to the Department of Dermatology for the diagnosis of erythematous skin lesions and erosions covered with haemorrhagic crusts located on the face (fig. 1 A), auricles, scalp, trunk (fig. 1 B) and lower limbs. Skin eruptions appeared more than a year ago. Exposure



**Figure 1.** Clinicopathological presentation of PF in an elderly woman. Erosions, some covered with crusts, on the face (A) and trunk (B). DIF visualized with blue light-emitting diode technology-operated microscopy revealed pemphigus IgG4(+++) deposits with a dew-drop on a spider web appearance in the epidermis (C). H + E-clusters of acantholytic exfoliating dyskeratotic cells (D). Both photomicrographs were taken at the original objective magnification of  $\times 40$

to sunlight exacerbated the dermatological condition. Mucous membranes were not involved. The patient was diagnosed with psoriasis 10 years earlier. In addition, she had a history of hypertension and atrial fibrillation. During hospitalization, a biopsy of the skin lesions from the back was performed for HPE. HPE revealed a slightly oedematous epidermis, undermined by a dense lymphocytic infiltrate. Clusters of disintegrated nuclei and acantholytic desquamated dyskeratotic cells could be seen on the epidermal surface in the loose stratum corneum. That may be consistent with PF. Confirmation of the diagnosis by immunopathology examination was indicated. A DIF of healthy perilesional skin was performed and pemphigus deposits of IgG(+), IgG4(+++) (fig. 1 C) and C3(+) in the epidermis were revealed. An ELISA test (autoimmune blistering diseases 6-antigen panel, Euroimmun, Germany) was performed and IgG to DSG1 were elevated (level 7.13, cut-off 1.0). A PF diagnosis was given based on the clinical picture, as well as the microscopic and immunological tests.

In addition, deviations in the examinations performed meant the patient also tested positive in a *Treponema pallidum* screening test (antibodies), had a positive TPHA result in a titre of 1 : 80, and positive RPR in a titre of 1 : 1, ELISA *Treponema pallidum* IgG (positive) and IgM (negative), indicating a history of syphilis.

The patient was treated with metoprolol, which could potentially cause skin lesions with PF morphology. After metoprolol was discontinued, indapamide was introduced, which proved unfortunate as this drug too could potentially induce pemphigus lesions. Eventually, this drug was also discontinued, and perindopril, a drug from the angiotensin-converting-enzyme inhibitors (ACEI) group, was prescribed. This drug has not yet been found to induce pemphigus, probably due to its thiol-free structure [5].

The patient was treated with oral methylprednisolone at a starting dose of 24 mg daily and topically with 0.05% clobetasol propionate ointment and 0.025% fluocinolone acetonide gel, achieving improvement of the skin lesions.

## DISCUSSION

The gold standard for a pemphigus diagnosis is a DIF test of the skin or mucous membranes. Serum immunological testing to determine the antigen recognized by autoantibodies is also necessary to establish the pemphigus type. According to the Polish Dermatological Society (PTD) guidelines for the diagnosis and treatment of pemphigus, HPE is not obligatory, but in specific cases it may be helpful and may facilitate diagnosis, especially in clinically ambiguous cases [6]. A 4–6 mm biopsy should be taken

from a new blister (up to 24 hours after appearing) or from the edge of a new erosion (blisters in PF being superficial within the upper epidermis, they rupture very easily, and only erosions may be seen), preferably using a “needle” method (“shave biopsy”) rather than performing a punch biopsy, which provides the opportunity to assess a larger section of the epidermis and the papillary layer of the skin, without the reticular layer of the dermis and subcutaneous tissue being unnecessary for diagnosis, and then the tissue should be fixed in 10% buffered formalin solution [7]. In the case of PF, an acantholytic subcorneal cleft is revealed in the granular layer or in the upper parts of the spinous layer. More commonly, the absence of a blister cover is observed, but individual acantholytic cells may be seen on the erosive surface. In longer-lasting skin lesions, the acantholytic cells become acidophilic as they age, resembling dyskeratotic cells. A characteristic of PF is the exfoliation of these acantholytic-dyskeratotic cells (fig. 1 D), different from the exfoliation of keratin scales in a normal stratum corneum. Acantholytic fissures and acantholytic dyskeratosis can also be revealed in hair follicles [8]. Assessment of these less obvious features requires experience in the histopathological diagnosis of pemphigus, and the clinician’s suggestion of a diagnosis of PF is particularly helpful. Neutrophils may accumulate in the contents of older subcorneal vesicles, on the surface of erosions, or in response to secondary superinfection, which may raise the suspicion of a number of diseases with subcorneal neutrophilic pustules [7]. According to European guidelines for the diagnosis of pemphigus, HPE, along with immunological tests, is required for the diagnosis of the disease [9]. The same criteria for the diagnosis of pemphigus are given in US guidelines [10]. The diagnostic management of AIBD in Poland, based mainly on DIF and serum immunological methods, is perceived as controversial and is questioned during the review process of articles on AIBD in foreign journals and during qualifying patients with AIBD for clinical trials, where HPE in the diagnosis is required. On the other hand, when the clinical picture is obvious and the diagnosis is confirmed by immunological examinations, taking an additional skin section for HPE, which may be difficult to interpret, especially by a pathologist without dermatopathological experience, can unnecessarily traumatize the patient and generate additional diagnostic costs. Therefore, the current diagnostic criteria in Poland appear to be more appropriate. It should be stressed that HPE cannot replace a well-performed DIF test in diagnosing AIBD. For patients exhibiting unequivocal clinical features of IgG-mediated AIBD, only a DIF test and a serum immunological examination are enough for diagnosis with a HPE being simply redundant. Still, according to an article by

Manocha *et al.*, a DIF test returned a positive result for 98% of patients diagnosed with PV, and a HPE revealed acantholysis in 95% of the tested patients [11]. These authors consider that HPE is as effective as other tools such as DIF and ELISA in diagnosing pemphigus [11]. However, such a point of view may be contested, because autoimmunity characteristic for both PV and PF cannot be detected by HPE.

When the scalp is involved in the course of PF, trichoscopy can be a helpful and non-invasive diagnostic method [12]. The following trichoscopy features may be found in PF: linear serpentine vessels, dotted vessels, arborizing vessels, yellow diffuse scaling, white diffuse scaling, white polygonal structures, yellow haemorrhagic crusts and yellow dots with a whitish halo ("fried egg mark") [12].

The co-occurrence of pemphigus and psoriasis, as seen in our patient, is rare. Possible reasons for the development of pemphigus in patients with psoriasis include the methods used to treat psoriasis, basement membrane abnormalities present in psoriasis, and common immunological mechanisms [13]. Therapies using topical anthralin, UVB radiation and PUVA may contribute to the destruction of the dermal-epidermal junction, increasing the possibility of autoantibody synthesis and the development of AIBD; indirectly, also the formation of anti-desmoglein antibodies [13, 14]. Moreover, the presence of

chronic inflammation characteristic of psoriasis, the transport of activated lymphocytes, and an increased number of antigen-presenting cells may expose and change basement membrane antigens, stimulating the production of antibodies targeting various epidermal epitopes [15].

Differentiating between psoriatic lesions and erythematous-exfoliative eruptions in PF, especially in the erythrodermic forms, may sometimes pose diagnostic difficulties. In such cases, HPE may facilitate the diagnosis. In the presented case, HPE of the skin lesions revealed features suggesting PF, but without one of its key presentations, namely separation/cleavage in the upper layers of the epidermis. No microscopic features of psoriasis were found.

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#### CONFLICT OF INTEREST

The authors declare no conflict of interest.

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