Autoimmune bullous dermatoses: should we treat the patient or the antibodies? A preliminary study

Serological detection of autoantibodies via indirect immunofluorescence (IIF) and enzyme-linked immunosorbent assays (ELISA) is usually helpful in the diagnostic process of autoimmune bullous dermatoses (AIBDs) [1]. ELISA provides objective and quantitative results, which may better reflect disease activity than those of IIF [1]. In fact, the titre of antibodies is reported to correlate with disease activity over time, especially anti-desmoglein (anti-Dsg) -1 and -3 in patients with pemphigus vulgaris (PV) and anti-BP180 in patients with bullous pemphigoid (BP). In contrast, the association between anti-BP230 titre and clinical course appears to be less evident [1, 2]. However, the association between titres of antibodies and disease activity and severity is still debated [3]. Should antibody titres guide therapeutic decisions or should they be based on clinical activity?

All patients who were diagnosed with BP or PV (histologically and/or based on laboratory findings) over a 12-month period were consecutively enrolled. They were evaluated clinically and their blood was collected for serology at T0, three months later (T1) and six months later (T2).

Clinical disease activity was given a score ranging 0-3. Patients with PV were given a score of 1 for moderate disease (Autoimmune Bullous Skin Disorder Intensity Score [ABSIS] <6.4), 2 for significant disease (6.4<ABSIS<31.5), and 3 for extensive disease (ABSIS>31.5) [4]. ABSIS was used rather than PDAI (Pemphigus Disease Area Index) because the latter has been validated as a score for PV with only 2 degrees of clinical severity [4]. Patients with BP were given a score of 1 for mild disease (Bullous Pemphigoid Disease Area Index [BPDAI] <20), 2 for moderate disease (20<BPDAI<57), and 3 for severe disease (BPDAI>57) [5]. When patients were free of mucocutaneous lesions, a score of 0 was given.

IIF was performed to detect anti-skin antibodies in patients' serum on monkey oesophagus substrate (BioSystems, Barcelona, Spain). The Mesacup-2 test desmoglein kit (Medical e Biological Laboratories, Nagoya, Giappone) was used for ELISA testing.

Clinical follow-up was continued for three years and relapses were recorded.

Thirty-six patients (26 with PV, 10 with BP) were evaluated at three timepoints (T0, T1 and T2). Clinical disease activity scores and laboratory results over time are reported in *table 1*.

Our results demonstrated a significant correlation between autoantibody titre and clinical activity for AIBDs, particularly PV, as both anti-Dsg-1 ($p<0.0001$) and anti-Dsg-3 titres (p=0.0004) reflected the clinical course of the disease. Moreover, the variation in autoantibodies titres between T0 and T2 correlated with variation in clinical activity scores ($p<0.0001$ for anti-Dsg-1, $p=0.0231$ for anti-Dsg-3). Moreover, IIF positivity was associated with higher clinical activity for PV ($p<0.0001$).

In patients with BP, we found that titres of anti-BP180 significantly reflected clinical activity scores ($p<0.0001$), however correlation between T0 and T2 was not significant ($p=0.3658$). Titre of anti-BP230, as well as IIF positivity, did not correlate with clinical course ($p = 0.8353$ and $p=0.8009$, respectively).

Furthermore, considering patients with disease activity of 0 at T2, subsequent clinical relapses were not linked to higher antibody titres. Namely, 5/8 PV patients and 2/3 BP patients who relapsed during three years of follow-up had negative antibodies at T2.

Overall, our results for both PV and BP reflect those of the available literature, endorsing once more the use of ELISA and IIF as useful tools during follow-up of patients with AIBDs. For PV, titres of anti-Dsg-1 and anti-Dsg-3, as well as their variation with time, and IIF positivity

Table 1. Clinical disease activity scores and laboratory results over time.

	Clinical Activity Index	Time			Lab	Time		
		T0	T1	T2		T0	T1	T2
PV (n=26)	Mean	1.92	1.36	0.90	Dsg-1 (RU/mL), median [IQR]	41.40 [0.00, 89.90]	0.00 [0.00, 99.00]	0.00 [0.00, 48.00]
	Median	2	1	0				
	SD	0.85	1.22	1.21	Dsg-3 (RU/mL), median [IQR]	115.25 [12.25, 159.77]	99.60 [0.00, 178.00]	36.00 [0.00, 147.00]
	IQR	1-2.75	0-2	0-1				
	Range	0-3	0-3	0-3	IIF positive, *n* (%)	21 [80.8]	13 [52.0]	14 [48.3]
BP (*n*=10)	Mean	2.5	1.2	0.8	BP180 (RU/mL), median [IQR]	64.80 [46.50, 83.07]	25.05 [13.00, 44.90]	20.50 [11.25, 39.60]
	Median	3	1	0.5				
	SD	0.71	0.79	1.03	BP230 (RU/mL), median [IQR]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]
	IQR	2-3	1-1	0-1	IIF positive, *n* (%)	2 [20.0]	1 [10.0]	0 [0.0]
	Range	1-3	0-3	0-3				

were all reliable indices of disease activity. For BP, titre of anti-BP180 reflected clinical activity; therefore, we consider it useful in monitoring disease activity during follow-up. Conversely, IIF positivity, titre of anti-BP-230 and variation of titres with time did not parallel disease activity.
An interesting novelty is that, in our small sample, when remission is achieved, antibody titre cannot be considered a predictor of relapse of AIBD. Therefore, considerations for therapy should not rely on this titre. Surely, these findings need to be confirmed in larger, multicentric studies. We are also continuing clinical and serological follow-up for these patients.
To answer our initial question: although some serological markers may overlap with disease activity, in our opinion, the clinical picture should guide our therapeutic decisions. ■

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Perforating pilomatricoma presenting as a cutaneous horn in a patient with myotonic dystrophy

Pilomatricoma is a type of common benign adnexal tumour that involves hair matrix differentiation and typically presents as a firm dermal or subcutaneous nodule covered with healthy skin. There are several clinical variants of pilomatricoma, and tumours with perforating channels through the epidermis have rarely been described as perforating pilomatricomas [1]. Herein, we report a case of perforating pilomatricoma with a cutaneous horn-like appearance in a patient with myotonic dystrophy type 1 (DM1).
A 77-year-old man presented with a three-month history of a growing mass on his right thigh. He was diagnosed with DM1 at 66 years of age after having gradually developed muscle weakness and myotonia. A physical examination revealed a slightly erythematous nodule on the right thigh; the nodule was 10 mm in diameter with a central hyperkeratotic protrusion that formed a cutaneous horn (*figure 1A*). No similar lesions were found elsewhere. Keratoacanthoma was suspected, and the lesion was completely excised. Histopathological examination results revealed a thick keratin layer on the surface containing focal calcification and parakeratotic cells forming the cutaneous horn (*figure 1B*). The base of the keratin layer revealed tumour nests consisting of basophilic basaloid cells and anucleated eosinophilic shadow cells in the upper dermis, exhibiting typical histological features of pilomatricoma (*figure 1C*). The basaloid cells had transformed into shadow cells and cornified into the cutaneous horn-like structure through a perforating epidermal channel (*figure 1D*). Based on these findings, the patient was diagnosed with perforating pilomatricoma. No skin lesion recurrence was observed two years following the tumour excision.
Perforating pilomatricoma is a rare variant of pilomatricoma that clinically presents as crusted or ulcerated nodules [2]. Perforating pilomatricomas are usually present in the upper dermis and even in the epidermis, and are more superficial than typical pilomatricomas. Previous reports have suggested that the superficial localization of the tumour predisposes them to perforate the epidermis through transepithelial elimination. Previously reported cases of perforating pilomatricoma have involved younger patients who developed pilomatricoma predominantly on the head, neck, upper trunk, and proximal upper limbs, which contrasts with our reported patient. A cutaneous horn can be formed due to various skin diseases, however, pilomatricoma is not usually a condition considered to cause the development of a cutaneous horn. One case report showed that a cutaneous horn was associated with pilomatricoma and the term "pilomatricomal horn" was proposed to describe it accordingly [3]. In our patient, we speculated that the central area of the nodule gradually increased due to transepithelial elimination through a perforating epidermal channel, similar to previously reported cases.
DM1, also known as Steinert disease, is a progressive, multisystem disorder characterized by muscle weakness, myotonia, cardiac conduction abnormalities, and cataracts. DM1 is also associated with an increased risk of skin neoplasms, predominantly pilomatricomas [4]. To our knowledge, this is the first report of perforating pilomatricoma presenting as a cutaneous horn in a patient with DM1. Most non-syndromic pilomatricomas develop due to a somatic activating mutation in the β-catenin gene, which encodes an intracellular signalling protein that regulates hair follicle development via Wnt signalling. DM1 is a hereditary disease due to the expansion of a cytosine-thymine-guanine (CTG) trinucleotide repeat in the 3'-untranslated region of the dystrophia myotonica protein kinase (*DMPK*) gene. In patients with DM1, it is