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Funding sources: none.

Conflicts of interest: A.P.F. is an investigator for Pfizer, Corbus, Mallinckrodt, Novartis and Roche Pharmaceuticals, and receives personal research support from Mallinckrodt and Novartis; honoraria from AbbVie, UCB, Novartis, Mallinckrodt and Celgene for consulting and advisory board participation; and honoraria from AbbVie, Novartis and Mallinckrodt for teaching and speaking.

This work was presented, in part, at the 2018 International Investigative Dermatology meeting on 17 May 2018 in Orlando, FL, U.S.A.

The clinical, immunological and pathological features for relapse of pemphigus herpetiformis: a univariate analysis of 26 cases

DOI: 10.1111/bjd.18518

Dear Editor, Pemphigus herpetiformis (PH) is a rare autoimmune blistering disease that accounts for only about 7% of all patients with pemphigus.[1] Various factors may contribute to PH relapse, requiring hospitalization and reintroduction of a high dose of the first-line drugs such as glucocorticoids, potentially leading to severe complications and high medical costs. Our study sought to identify the clinical, immunological and pathological characteristics of patients with PH, as well as the risk factors for relapse of PH. We designed a retrospective cohort study after reviewing the clinical charts of 43 patients and included 26 patients who were referred to our hospital, diagnosed with PH from 1984 to 2019, and followed up for a median of 2·5 years (range 0·33–29). The patients' data used for analysis include medical history, associated disease, dates of onset and diagnosis, type and localization of the lesions, immunological and pathological features, treatment, adverse effects of treatment, follow-up and outcome. The relapse rates were estimated using the Kaplan–Meier method (Table 1).

Typical skin lesions were annular urticated erythema with papules and blisters. Review of the histopathology revealed intraepidermal blisters with acantholysis and eosinophilic spongiosis, and microabscesses with eosinophilic and/or neutrophilic infiltration. Direct immunofluorescence (DIF) and indirect immunofluorescence (IIF; re-examined using archived serum samples) demonstrated deposition of IgGs (IgG1 and IgG4) or/and C3 on keratinocyte cell surfaces. Diagnosis of PH was confirmed in 26 of the 43 patients, as proposed previously.[2,3]

The average age of the 26 patients (14 male and 12 female) was 56·6 years (range 15–87). Initial misdiagnosis before pathological and immunological examinations occurred in 73% of the patients (19 of 26), with dermatitis herpetiformis and bullous pemphigoid being the most common ones. Most patients (77%) had lesions covering ≥ 60% of their whole skin during onset. Other clinical features of PH included erythema annulare (27%, seven of 26), positive Nikolsky sign (38%, 10 of 26) and mucosal involvement (23%, six of 26). Comorbidities with other diseases upon diagnosis were observed in 54% of the patients. The average duration of hospitalization was 14·6 days. Corticosteroids were administrated as the first-line treatment in 77% of the patients (20 of 26).

Eleven patients had positive desmoglein (Dsg)1-specific antibodies (four of them > 150 U mL^{-1}). Three patients had positive Dsg3-reactive antibodies, and two of them also had positive Dsg1 antibodies. Twenty patients showed intercellular IgG deposition by DIF, five had negative results and one patient had C3 deposited along the basement membrane zone. Of the 25 patients tested with IIF, 22 had positive results and three had negative results. Sera of 18 patients were available for further investigation into the subclasses of IgGs by IIF. We found that eight patients had binding of both IgG1 and IgG4 antibodies, four patients had only IgG1, and one patient had only IgG4. Four patients had negative results for both IgG1 and IgG4. Notably, one patient had class-switch of IgG from IgG1 to IgG4 in 22 days, along with an elevation of the IIF titre from 1 : 80 to 1 : 160. The IgG4 subclass is considered to be the predominant isoform in pemphigus vulgaris and is related to disease activity, whereas IgG1 can be associated with disease remission.[4] Switch of the IgG1 and IgG4 subclasses may not directly interfere with their binding properties,[5] but it may affect the disease pathology.

The overall relapse rate during follow-up was 27% (seven of 26). The results are consistent with previous work regarding seven patients with PH, of whom two patients

Table 1 Log-rank and Cox univariate analyses for relapse in patients with pemphigus herpetiformis

			Univariate analysis		
	Patients	Patients with relapse	Hazard ratio (95% CI)	P-value[b]	P-value[c]
Age (years)					
≥ 62	13	6	7·72 (0·93–64·3)	0·059[d]	0·025[d]
< 62	13	1			
Sex					
Male	14	4	1·14 (0·25–5·10)	0·87	0·87
Female	12	3			
Disease severity[a]					
Severe	20	6	1·97 (0·24–16·5)	0·53	0·53
Mild	6	1			
Erythema annulare					
Yes	7	3	2·61 (0·58–11·7)	0·21	0·19
No	19	4			
Positive Nikolsky sign					
Yes	10	4	4·47 (0·96–20·8)	0·057[d]	0·039[d]
No	16	3			
Mucosal involvement					
Yes	6	3	2·94 (0·65–13·3)	0·16	0·14
No	20	4			
Combination of diseases					
Yes	14	4	1·23 (0·27–5·50)	0·79	0·79
No	12	3			
Elevation of eosinophils in blood (> $0·8 \times 10^9$ cells L^{-1})					
Yes	5	3	4·51 (1·00–20·4)	0·050[d]	0·032[d]
No	21	4			
Percentage of eosinophils in blood > 8%					
Yes	6	4	4·09 (0·91–18·4)	0·066[d]	0·047[d]
No	20	3			
Direct immunofluorescence					
Positive	22	5	0·44 (0·084–2·31)	0·33	0·32
Negative	4	2			
Indirect immunofluorescence					
< 1 : 40	5	4	5·95 (1·31–27·0)[d]	0·021[d]	0·009[d]
≥ 1 : 40	21	3			
Eosinophil infiltration in pathology					
Yes	20	5	0·84 (0·16–4·34)	0·83	0·83
No	6	2			
Time before effective treatment					
≥ 5 months	15	6	4·71 (0·57–39·2)	0·15	0·11
< 5 months	11	1			
Combination therapy					
Yes	22	7	26·2 (0·003–28869)	0·48	0·27
No	4	0			
Time of admission					
≥ 15 days	14	5	2·63 (0·51–13·7)	0·25	0·23
< 15 days	12	2			
Corticosteroid-related infection					
Yes	3	1	1·14 (0·14–9·52)	0·90	0·90
No	23	6			
Effective corticosteroid dose					
> 40 mg	11	3	1·07 (0·24–4·81)	0·93	0·93
≤ 40 mg	15	4			

CI, confidence interval. [a]Severe: lesions covering ≥ 60% of the whole skin during onset; mild: lesions covering < 60% of the whole skin during onset. [b]P-value in Cox analysis. [c]P-value in Kaplan–Meier analysis. [d]Significant values according to our methods.

(two of seven, 29%) had relapse after treatments,[6] supporting that PH had a relatively better prognosis than the canonical pemphigus, pemphigus vulgaris and pemphigus foliaceus.[7] Moreover, most of the relapses in our patients with PH (71%, five of seven) were found to occur during the first 2 years after remission, and all these relapses

occurred during withdrawal of medicines. This suggests that careful tapering of the dosage of corticosteroids with follow-up for 2 years after remission is essential. Statistical analysis revealed that age ≥ 62 years (P = 0·025), positive Nikolsky sign (P = 0·039), elevated peripheral blood eosinophil count (> $0{\cdot}8 \times 10^9$ cells L^{-1} and > 8% of peripheral blood mononuclear cells in peripheral blood; P = 0·032 and P = 0·047, respectively) and lower circulating autoantibody titre (< 1 : 40 by IIF; P = 0·009) are significantly related to relapse. The relapse rates appear higher in patients whose effective treatments were delayed for ≥ 5 months of diagnosis (P = 0·11) or who were hospitalized for ≥ 15 days (P = 0·23), although no statistically significant differences were found.

In conclusion, our study draws attention to frequent misdiagnosis in this rare variant of pemphigus and proposes careful tapering of therapeutic drugs for the first 2 years of diagnosis due to risk of relapse. Further investigation by a multicentric study with a larger sample size is necessary to support our results.

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Funding sources: this work was supported by the Milstein Medical Asian American Partnership Foundation, Education Reform Projects of Peking Union Medical College (no. 2016zlgc0106), the National Natural Science Foundation of China (81972945) and Beijing Municipal Natural Science Foundation (7192166).

Conflicts of interest: none.

Musculoskeletal ultrasound can improve referrals from dermatology to rheumatology for patients with psoriasis

DOI: 10.1111/bjd.18515

Dear Editor, Psoriasis affects 1–3% of the population, and up to one-third of patients with psoriasis have underlying psoriatic arthritis (PsA).[1] Nonspecific musculoskeletal complaints are even higher, occurring in around 50% of patients.[2] Detecting early signs of PsA and providing early treatments are crucial to prevent progressive, damaging arthritis.[3] Due to the high frequency of nonspecific pain in psoriasis, it is not possible for every patient with psoriasis with joint pain to be assessed by a rheumatologist. Different screening tools have been developed for the dermatology practice to distinguish patients with a higher likelihood of having PsA; however, the low specificities of these tools limit their use in clinical practice.[4–6]

Musculoskeletal ultrasound (US) has been shown to be more sensitive than physical examination to detect joint inflammation.[7] It has been used commonly in rheumatology practice for diagnosis and follow-up of patients with inflammatory arthritis including PsA. We hypothesize that a screening US could add value to improve referrals from dermatology to rheumatology for patients with psoriasis with joint pain.

To test our hypothesis a prospective study on patients with psoriasis with any joint pain was carried out (Ottawa Health Science Network Research Ethics Board, Ottawa: 20160386-01H). Exclusion criteria included already known diagnosis of PsA, recent trauma or surgery of the painful joints, and pregnancy. After giving informed consent, patients had an US scan on the same day as their clinical assessment by one of two experienced rheumatologists in musculoskeletal US, blinded to the clinical examination findings (S.B. or D.S.). A predefined limited US protocol was performed, examining the wrists and 2–3rd metacarpophalangeal, 2–3rd proximal interphalangeal and 2–5th metatarsophalangeal joints for synovitis, and also Achilles enthesitis and the most painful joint. The US scoring system included a semiquantitative scoring of inflammation (none, mild, moderate, severe) for both grey-scale and Doppler findings. A similar approach was used to compare the inflammatory entheseal findings.

The Early Arthritis for Psoriatic Patients[6] and Psoriasis Epidemiology Screening Tool[5] questionnaires were completed by the patients. After reviewing these questionnaires the dermatologist was asked to make a decision on the indication to be