Secukinumab in pityriasis rubra pilaris: A case series demonstrating variable response and the need for minimal clinical datasets

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INTRODUCTION

Pityriasis rubra pilaris (PRP) is a heterogeneous group of rare papulosquamous disorders characterized by folliculocentric keratinization.[1] PRP has a bimodal incidence with equal gender predilection.[1] It can be spontaneous in nature and associated with familial inheritance or as a paraneoplastic phenomenon.[1,2] PRP has a variable clinical presentation with Griffiths criteria classifying PRP into 5 subtypes based on age of onset, clinical course, and prognosis.[1] HIV-related PRP and paraneoplastic PRP have been proposed as additional subtypes.[2] The pathophysiology of PRP remains unclear but is proposed to be triggered by a variety of as-yet-unidentified triggers of chronic inflammation.[3] Reported effective treatment with etanercept, adalimumab, ustekinumab, and secukinumab[4-11] implicate tumor necrosis factor α, interleukin (IL)-12/IL-23, and IL-17[5,12] as involved in the downstream inflammatory cascade, although the variability in response indicates some degree of disease heterogeneity within Griffiths subtypes. Feldmeyer et al[12] demonstrated upregulation of helper T cell 17 cytokines including IL-17A, IL-17F, and IL-22 in lesional skin of a patient with PRP who demonstrated a rapid resolution of disease with ustekinumab.[12] Ustekinumab has also been reported as particularly beneficial in patients with CARD14 polymorphisms.[13]

Abbreviations used:

CLL: chronic lymphocytic leukemia
IL: interleukin
PRP: pityriasis rubra pilaris

We present a case series of 3 patients with clinical and histologic diagnoses of PRP treated with subcutaneous secukinumab per the dosing regimen for chronic plaque psoriasis (300 mg weekly on weeks 0, 1, 2, 3, and 4 and 300 mg every 4 weeks thereafter). All 3 patients had disparate clinical responses highlighting the need for further translational investigation into the pathophysiologic heterogeneity of the disease and consideration of revision of Griffiths subtyping of PRP to align with pathophysiology and treatment response rather than age of onset and extent of disease.

CLINICAL INFORMATION

Patient A, a 52-year-old man, presented with a 4-week history of rostro-caudal progression of erythema associated with palmoplantar keratoderma and nail changes. His history was relevant for type 1 diabetes mellitus controlled with insulin glargine and he denied any family history of PRP or psoriasis. He had no previous systemic treatment for his condition. Histopathology testing found vertical and horizontal

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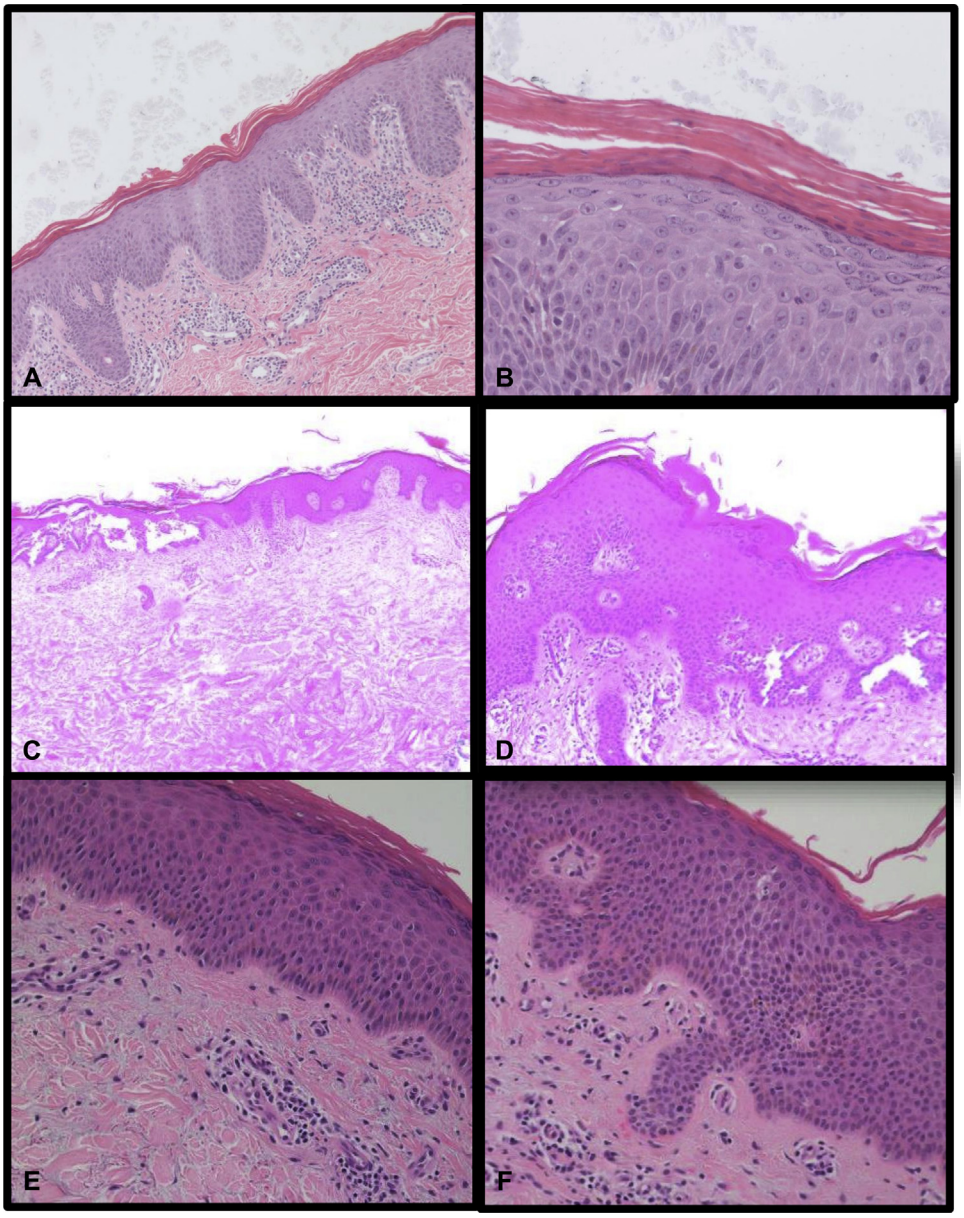

Fig 1. Histopathology of patients included in this case series. Patient A (**A** and **B**), patient B (**C** and **D**), and patient C (**E** and **F**). **A**, Hyperkeratosis with moderate irregular acanthosis and a moderate perivascular inflammatory infiltrate in the papillary dermis. **B**, Alternating orthokeratosis and parakeratosis with thickened suprapapillary plates. **C**, Irregular acanthosis with acantholysis. **D**, Orthokeratosis and parakeratosis. **E**, Compact orthokeratosis with focal parakeratosis. **F**, Some focal acantholysis is evident with perivascular lymphocytic infiltrate. (**A-F**, Hematoxylin eosin stain; Original magnifications: **A**, ×40; **B**, ×200; **C**, ×20; **D**, ×40; **E**, ×100; **F**, ×100.)

alternating orthokeratosis and parakeratosis consistent with PRP (Fig 1). Full-body computed tomography scan and blood work did not find any suggestions of occult neoplasia. His PRP was classified as Griffiths type 1.

Patient B, a 71-year-old man, presented with a 4-year history of erythroderma, including scalp involvement and palmar keratoderma associated with a concurrent diagnosis of chronic lymphocytic leukemia (CLL) under the care of a hematologist. His condition was recalcitrant to methotrexate, acitretin, cyclosporine, fumarates, narrow-band ultraviolet B therapy, and oral steroids. His CLL was stable for the last 3 months treated with ibrutinib. Multiple biopsy

Table I. Demographic and clinical details pertaining to the case reports of patients A, B, and C at baseline (week 0) and up to week 24 of treatment

Demographics				IGA				DLQI				% BSA			
Patient	Age, y	Gender	Griffiths subtype	Wk 0	Wk 4	Wk 12	Wk24	Wk 0	Wk 4	Wk 12	Wk24	Wk 0	Wk 4	Wk 12	Wk 24
A	52	M	1	9	3	1	0	24	21	12	7	90	54	28	0
B	71	M	1	9	7	7	7	28	27	28	26	85	85	80	80
C	61	M	2	4	6	WH	4	20	28	WH	16	36	45	WH	25

BSA, Body surface area; *DLQI*, dermatology life quality index; *IGA*, investigator global assessment; *WH*, withheld.

specimens were taken with findings of epidermal spongiosis, mild acanthosis, and superbasilar and intraepithelial acantholysis (Fig 1). Review of biopsies found previously unappreciated vertical and horizontal alternating orthokeratosis and parakeratosis (Fig 1) consistent with PRP. His PRP was classified as Griffiths type 1 (paraneoplastic).

Patient C, a 61-year-old man, presented with a 30-year history of localized plaques of erythema with folliculocentric plugging and scale to the arms, legs, and buttocks. His condition was resistant to topical steroids, oral methotrexate, ultraviolet B therapy, and acitretin. Multiple skin scrapings and tissue cultures were negative for fungi. Histopathology found orthokeratosis and parakeratosis with intraepidermal acantholysis (Fig 1). Periodic acid—Schiff staining of biopsied tissue failed to identify evidence of fungal infection. Considering the lack of response to conventional treatments, the histopathology slides were reviewed and suggested subtle signs of a diagnosis of PRP. Full-body computed tomography scan and blood work did not find occult neoplasia. His PRP was classified as Griffiths type 2.

Further clinical details are presented in Table I and Fig 2. Histopathologic slides are presented in Fig 1. All patients were treated after completing full clinical workup for biologic treatment per current guidelines[14] and undergoing an age-appropriate malignancy screen based on clinical history and examination. Patient B underwent consultation with his treating hematologist to ensure that no interference with current treatment for his CLL was anticipated. All patients were treated for a total of 6 months, at which point, if complete clinical response was achieved, the drug was withdrawn to assess rates of recurrence. Blood tests were undertaken every 2 weeks until week 8, with monthly blood tests thereafter. No expected adverse events (upper respiratory tract symptoms, injection site reactions) were seen across the 3 patients. Clinical improvement was seen in patient A by week 4 of therapy with clearing in a rostro-caudal progression. At the time of publication, patient A has had no recurrence of symptoms 3 months after cessation of secukinumab. Patient B had a partial response, and his CLL remained stable throughout the 6 months of therapy. Patient C had a paradoxical worsening during the first 8 weeks of therapy leading to temporary treatment withdrawal for 4 weeks. Resumption of treatment at patient request did not lead to further worsening of disease and resulted in partial improvement over the next 12 weeks (Table I).

DISCUSSION

This case series combined with previous case reports suggest that secukinumab can be a rapid and effective option for complete clearance of type 1/type 2 PRP. In the setting of complete rapid clinical response to secukinumab in type 1 PRP, withdrawal of the drug after complete disease control does not result in recurrence of symptoms. This finding leads to the suggestion that the role of biologic therapy in type 1 PRP is to fast-track the resolution of the inflammatory cascade potentiated by the unknown (but presumably singular) trigger event. The lack of complete response in cases, including those associated with positive family history of PRP or paraneoplastic cases, suggests that an underlying recurrent inflammatory trigger remains present. It is yet unknown if a proportion of PRP patients do not respond to IL-17 antagonists, and if this is indicative of alternate inflammatory pathways being involved in the pathogenesis of disease. Publication bias in the reporting of dramatic responses of PRP to biologic therapy makes assessment of these cases problematic outside of a large multicentre cohort study. The stability in the status of CLL in patient B also suggests that in this case, treatment with secukinumab and concomitant ibrutinib does not result in any untoward adverse events or progression of pre-existing CLL.

Further translational efforts are required to consistently assess baseline levels of inflammatory cytokines in PRP patients treated with biologic therapies. A proposed minimum clinical dataset[15] (Table II) would also begin to standardize reports of biologic therapy in PRP to guide further immunopathogenic

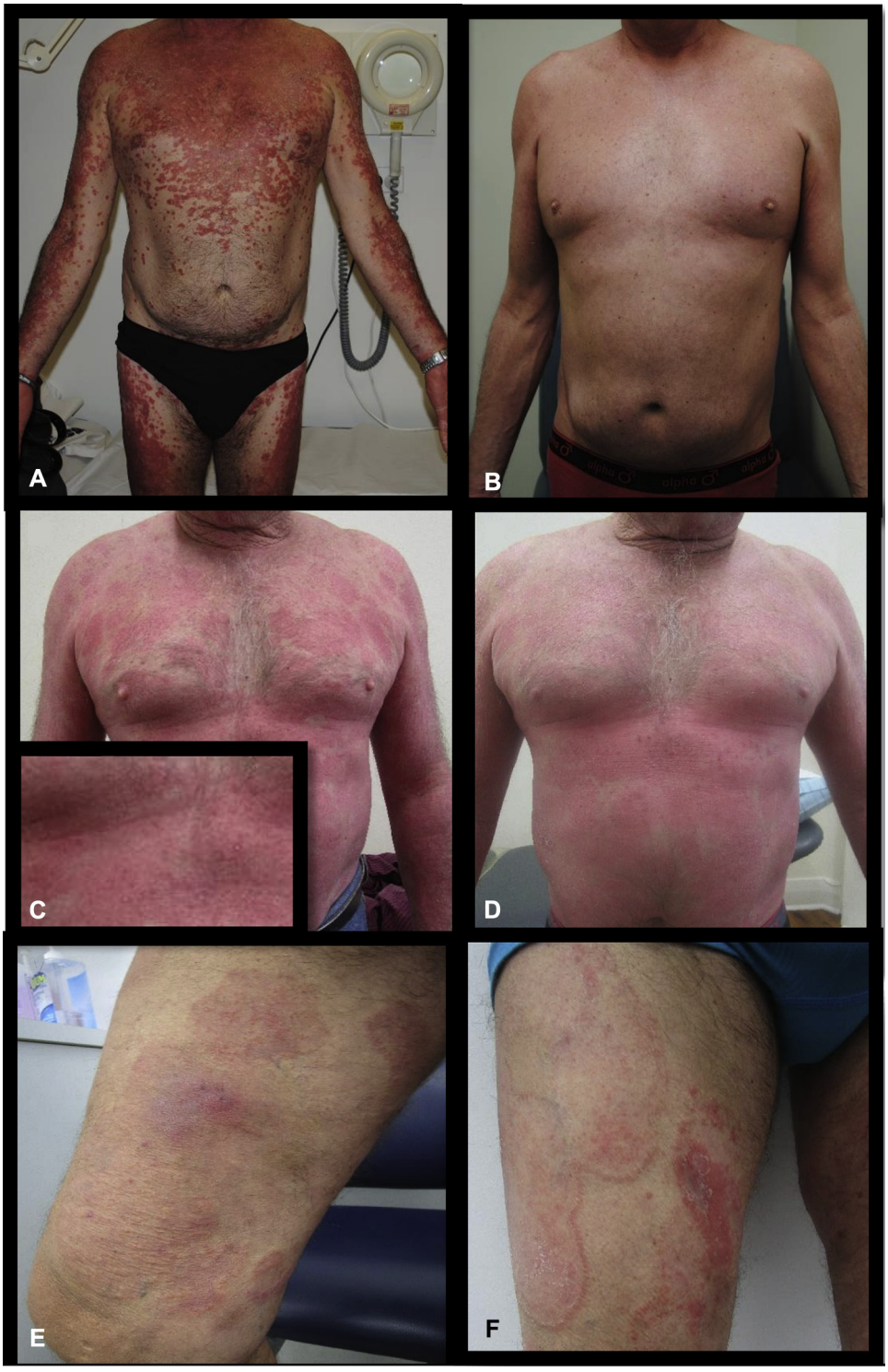

Fig 2. Variability in response to secukinumab for clinically and histologically diagnosed PRP. **A**, Patient A week 0. **B**, Patient A week 24. **C**, Patient B week 0. **D**, Patient B week 8. **E**, Patient C week 0. **F**, Patient C week 8. Patient B had paraneoplastic PRP secondary to CLL and had only limited response to secukinumab over a 6-month period. Patient A had rapid and complete response with no evidence of disease recurrence up to 6 months after cessation of secukinumab. Patient C had paradoxical worsening of disease and ceased treatment at week 8.

Table II. Proposed minimal clinical dataset for the treatment of PRP using biologic agents including all reported cases of treatment with secukinumab (including the 3 reported cases)

									Treatment history			Baseline quality of life assessment	Clinical endpoints			
													Percentage of body surface area improvement	PASI	Time to response	AE
Case	Reference	Patient age at onset	Patient gender	Time since disease onset	Griffiths subtype of PRP	Medical comorbidities	FHx Pso	FHx PRP	Prior treatment	Prior response	AE	NR	100	NR	2 wk	NR
1	Kevric[8]	54	F	52 y	V	NR	NR	NR	MTX Isotretinoin Acitretin Infliximab Adalimumab	Limited Limited Limited Limited Limited	NR	NR	100	NR	2 wk	NR
2	Gauci et al[9]	33	F	9 y	II	Vesicoureteral reflux, hydronephrosis	No	No	Acitretin Cyclosporin MTX Infliximab Ustekinumab IVIG Omalizumab Prednisolone	Minimal Partial Minimal Minimal Minimal Minimal Minimal Good	NR	NR	NR	27.6-5.6	4 wk	Oral & esophageal candidiasis
3	Schuster et al[10]	67	M	Acute	I	NR	No	No	Acitretin	Minimal	NR	NR	100	NR	8 wk	NR
4	Mariasy et al[11]	68	M	Several wk	I	NR	NR	NR	MTX Acitretin Apremilast NBUVB	Minimal Minimal Good Minimal	NR	NR	100	NR	6 mo	NR
5	Patient A	52	M	4 wk	I	T1DM	No	No	Nil	NA	NA	24/30	100	NR	14 wk	Nil
6	Patient B	71	M	4 y	I (Paraneoplastic)	CLL	No	No	MTX Acitretin Cyclosporin NBUVB	Minimal Minimal Minimal Minimal		28/30	20	NR	NA	Nil
7	Patient C	61	M	30 y	II	Nil	Yes	No	MTX Acitretin NBUVB	Minimal Minimal Minimal		20/30	11	NR	NA	Worsening

AE, Adverse events; *FHx*, family history; *MTX*, methotrexate; *NA*, not applicable; *NBUVB*, narrowband ultraviolet B; *NR*, not reported; *pso*, psoriasis; *T1DM*, type 1 diabetes mellitus.

stratification of disease and eventual revision of Griffiths' taxonomy. This would also hopefully lead to more targeted therapy and predictable clinical outcomes for patients suffering with PRP.

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