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Pyoderma gangrenosum, acne, and suppurative hidradenitis syndrome in end-stage renal disease successfully treated with adalimumab

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Abstract

PASH syndrome (pyoderma gangrenosum, acne, and suppurative hidradenitis) forms part of the spectrum of autoinflammatory diseases. We report an unusual case of PASH syndrome in a patient with end-stage renal disease (ESRD) who was successfully treated with the tumor necrosis factor inhibitor, adalimumab. The case underscores the challenges associated with the treatment of PASH syndrome as well as the ongoing search to establish a genetic basis for the syndrome. Renal impairment has been reported in association with pyoderma gangrenosum but has not been described in PASH syndrome. We believe this to be the first reported case of a patient who developed PASH syndrome in the setting of ESRD.

Keywords: pyoderma gangrenosum, acne, and suppurative hidradenitis, PASH syndrome, adalimumab, end-stage renal disease

Introduction

The clinical triad pyoderma gangrenosum (PG), Acne, and hidradenitis suppurativa (HS), known as PASH syndrome, is a recently described entity that forms part of the spectrum of autoinflammatory diseases (ADs), [1]. ADs are a set of illnesses that cause systemic inflammation due to a dysregulation in the innate immune system [2]. We report a case of PASH syndrome in a patient with end-stage renal disease (ESRD) who was successfully treated with the tumor necrosis factor (TNF) inhibitor, adalimumab.

Case Report

A 42-year-old man presented with a 2-year history of painful skin lesions affecting his upper and lower extremities, trunk, and groin area. The lesions started out as pustules, coalesced into abscesses, and eventually broke down to form ulcers. The patient's medical history was significant for ESRD owing to focal segmental glomerulosclerosis with subsequent hypertension. Chronic medication consisted of furosemide, amlodipine, and atenolol.

He had been suffering from acne since the age of 16 and was diagnosed with HS at age 30, which was surgically treated in both axillae. He denied any relevant family history of skin disease. On systemic review the patient reported no constitutional symptoms and specifically denied arthralgia or gastrointestinal (GI) symptoms.

He consulted numerous primary care physicians over the course of 2 years, who treated him with multiple antibiotics and antifungals with no response. He was also prescribed a superpotent topical steroid (clobetasol propionate 0.05% ointment) with a partial response.

On physical examination, he had multiple erythematous plaques consisting of nodules, abscesses, draining sinuses, ulceration, and cribriform scarring distributed over both upper extremities and inner thighs (**Figure 1** A). Surgical scars were evident

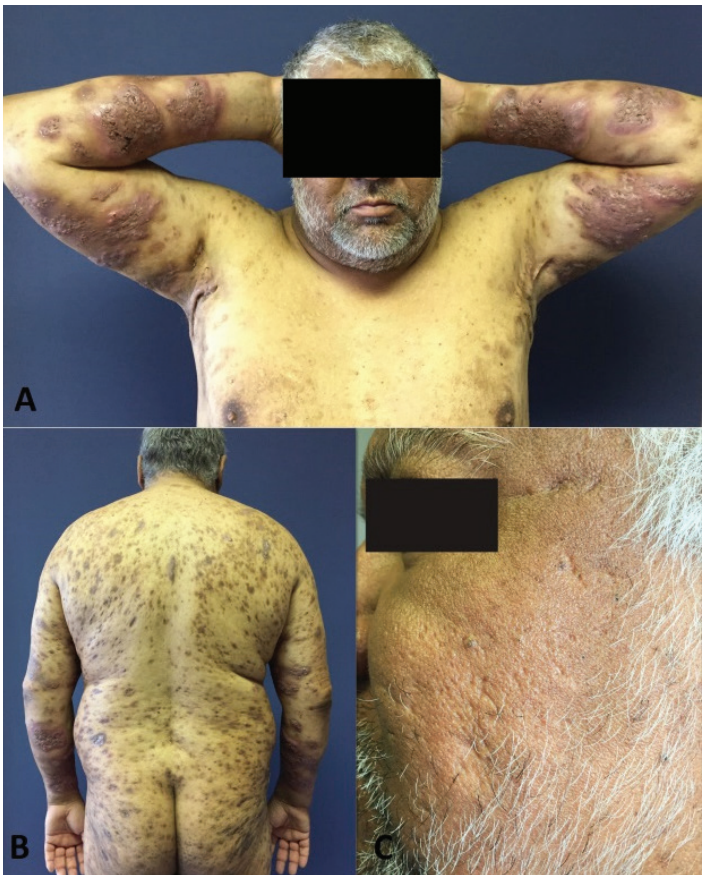

Figure 1. *A) Multiple erythematous plaques consisting of nodules, abscesses, draining sinuses, ulceration and cribriform scarring distributed over both upper extremities. Surgical scars are evident in both axillae from previous hidradenitis suppurativa surgery. B) Multiple comedones and post inflammatory hyperpigmentation over his back. C) Prominent acne scarring was also visible on his face.*

in both axillae (**Figure 1**A) with active Hurley stage III HS in the inguinal area. Prominent acne scarring was also visible on the patient's face (**Figure 1**B) and he had multiple comedones and post inflammatory hyperpigmentation over the chest and back (**Figure 1**C).

Histological examination of biopsies taken from the lesions on his upper extremities showed nodular suppurative granulomatous inflammation with sinus formation (**Figure 2**). Special stains to rule out infections were all negative including a Ziehl-Neelsen, Brown-Hopps gram, and periodic acid-Schiff stain.

Bacterial culture showed only mild growth of Proteus mirabilis, which was considered as secondary colonization. Mycology culture of tissue showed no fungal growth.

A diagnosis of PG was made based on the histology and the clinical presentation of painful chronic erythematous plaques, with sinus formation and shallow ulceration. Other causes of cutaneous ulceration were ruled out and the patient fulfilled international proposed criteria for the vegetative subtype of PG [3]. In the setting of acne and HS the patient was diagnosed with PASH syndrome.

The patient was further investigated to rule out any PG-associated disease. A lower gastrointestinal endoscopy ruled out any inflammatory bowel disease and serum and urine protein electrophoresis showed no signs of hematologic malignancy or monoclonal gammopathy. The rheumatoid factor was negative.

Genetic studies in this patient involved whole exome sequencing with a specific focus on variants in genes

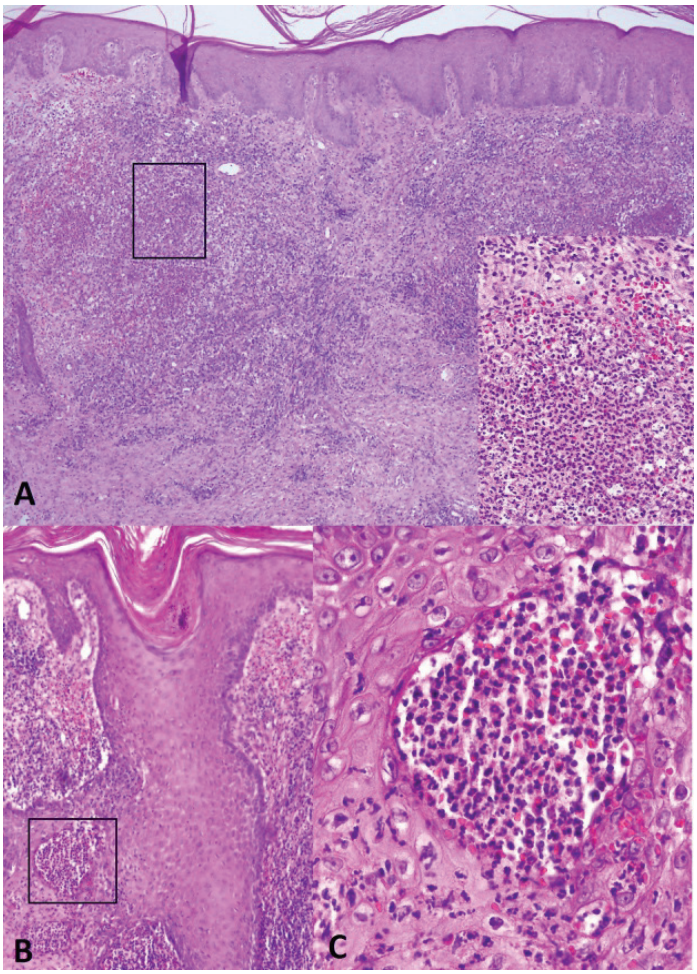

Figure 2. *A) Nodular infiltrate of suppurative granulomatous inflammation. H&E, 4%. B) Follicular plugging, marked hyperplasia of follicular epithelium and a dense infiltrate of lymphocytes, macrophages, plasma cells and neutrophils. H&E, 4%. C) Intraepithelial pustule-containing mature neutrophils. H&E, 10%.*

Table 1. *Genes involved in inflammatory pathways and skin diseases.*

Year	Disease	Gene
1997	Familial Mediterranean Fever (FMF)	MEFV
1999	TNF-Receptor Associated Periodic Syndrome (TRAPS)	TNFRSF1A
1999	Hyper IgD Syndrome (HIDS)	MVK
2001	Cryopyrin Associated Periodic Syndromes (CAPS)	NLRP3 (CIAS1)
2001	Blau Syndrome	NOD2
2001	Cherubism	SH3BP2
2002	Pyogenic sterile Arthritis, Pyoderma gangrenosum and Acne (PAPA)	PSTPIP1
2004	Early Onset Sarcoidosis (EOS)	NOD2
2005	Majeed Syndrome	LPIN2
2006	Recurrent Hydatidiform Mole 1 (RHM1)	NLRP7
2008	Familial Cold Autoinflammatory Syndrome 2 (FCAS2)	NLRP12
2009	Deficiency of IL-1 Receptor Antagonist (DIRA)	IL1RN
2009	Severe infantile inflammatory bowel disease	IL10RA, IL10RB, IL10
2011	CANDLE/JMP/NNS	PSMB8
2011	Deficiency of IL36 Receptor Antagonist (DITRA)	IL36RN
2012	Autoinflammation & PLCγ2-associated antibody deficiency & immune dysregulation (APLAID)	PLCG2
2012	HOIL1 Deficiency	RBCK1 (HOIL1)
2013	Pustular psoriasis/ pityriasis rubra pilaris	CARD14

previously reported in inflammatory pathways and autoinflammatory syndromes (**Table 1**). The variants that were identified in these genes (**Table 2**), however, are all commonly found in the general population (allele frequency > 1%).

The patient was initiated on prednisone 40mg once daily and doxycycline 100mg twice daily. He was encouraged to continue with topical clobetasol propionate 0.05% ointment and to use an antibacterial wash in the areas affected by HS.

After 4 months, the patient's PG showed significant improvement on this treatment but the HS lesions only showed partial improvement with persistent drainage from the inguinal area.

Table 2. *Genes with common variants that were identified in the patient.*

Gene	Variant
CARD14	R547S
IL10RA	R351G
MEFV	G436R
	D424E
NLRP7	G487E
	V391I
NOD2	P268S
	R702W
PSMB8	G8R

As a consequence of the long-term high dose systemic corticosteroid intake he developed a significant GI hemorrhage, requiring blood transfusion and hospitalization; he developed prominent cushingoid features.

Prednisone was weaned. Simultaneously doxycycline was changed to rifampicin 600mg daily and clindamycin 300mg BID. The patient's PG flared owing to the reduced dose of prednisone and the HS lesions did not respond to the change in antibiotics. Because of the patient's renal impairment conventional immunosuppressive drugs like methotrexate and cyclosporine were contraindicated and he was commenced on adalimumab. This was given 160 mg subcutaneously at week 0, 80 mg at week 2, and 40 mg weekly for weeks 4-8.

The patient showed a remarkable response at 8-weeks (**Figure 3**). He experienced complete remission of his PG lesions and achieved a Hidradenitis Suppurativa Clinical Response (HiSCR). HiSCR is defined as a ≥ 50% reduction in inflammatory lesion count and no increase in abscesses or draining fistulas in HS when compared with baseline [4].

Case Discussion: PASH syndrome was first described by Braun-Falco et al. in 2012 as a new autoinflammatory

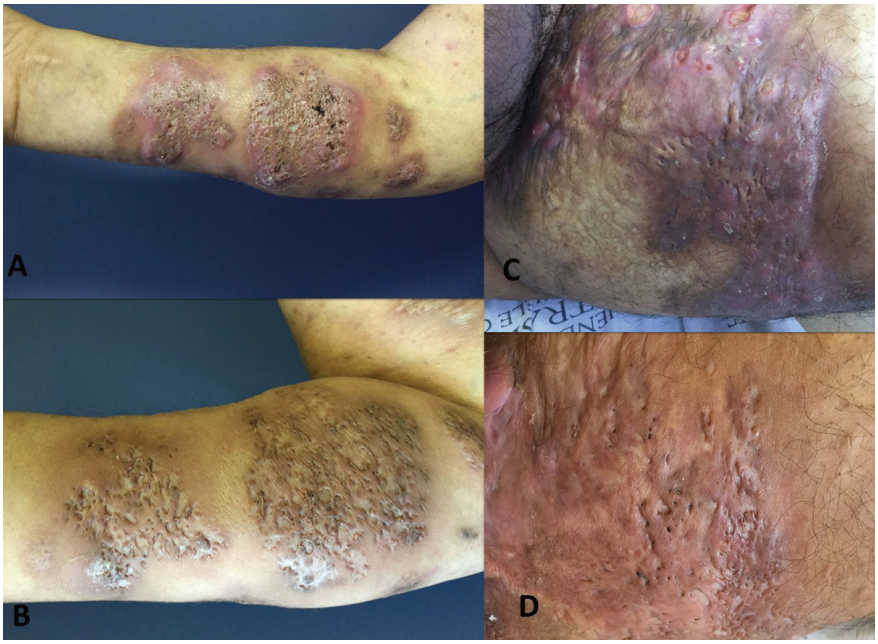

Figure 3. *PG and HS lesions showing marked improvement after 8 weeks of adalumimab treatment. Right forearm at diagnosis (A) and at 8 weeks (B). Left upper thigh at diagnosis (C) and at 8 weeks (D).*

syndrome related to PAPA syndrome (Pyogenic Arthritis, Pyoderma gangrenosum, and Acne) but distinct owing to the absence of pyogenic arthritis and an association with HS [1].

Monogenic ADs are associated with different mutations in the interleukin-1β (IL-1β) pathway, leading to an overproduction of IL-1β. This triggers the release of proinflammatory cytokines and chemokines, which leads to the recruitment and activation of neutrophils, causing a neutrophil-mediated inflammation [4].

Immunological studies confirmed this over expression of the main proinflammatory cytokines in PG lesions of PASH patients namely IL-1β and its receptors, TNF and IL-17 [5].

Although mutations in genes commonly associated with ADs have been identified in PASH syndrome (**Table 3**), a genetic basis for the syndrome is still not fully established [6, 7]. Our genetic analysis identified some common variants in genes previously reported in inflammatory pathways and ADs but failed to identify a definitive causative factor. An increased number of CCTG repeats in the PSTPIP1 promotor was reported in the first two cases of PASH syndrome [1] but this was not demonstrated in this patient.

PG can be associated with inflammatory bowel disease, hematological malignancies, monoclonal gammopathy and rheumatoid arthritis but extensive investigations ruled these out. An association of PG and ESRD has been described in isolated case reports [8, 9] and a retrospective study that analyzed data from 49 patients with pyoderma gangrenosum showed that 18.4 % had renal insufficiency [10]. Despite this established association between PG and renal impairment we believe this to be the first reported case of PASH syndrome in a patient with ESRD.

ESRD gives rise to various cytokine disturbances and to a state of hypercytokinemia owing to reduced removal rate as well as increased cytokine generation [11]. Whether this contributed to the clinical manifestations of PASH syndrome in our patient remains to be proven.

The treatment of PASH syndrome remains problematic as conventional immunosuppressive therapies often fail to provide satisfactory results [7]. In our case some of the PG lesions showed a response to topical clobetasol propionate 0.05% ointment. This supports recent evidence that PG may be controlled effectively using topical agents like superpotent topical steroids, depending on the size of the lesion [12]. The patient showed significant improvement in his PG lesions in response to a combination of systemic corticosteroids and doxycycline, but the HS lesions only showed a partial response.

Isolated case reports showed the TNF inhibitors infliximab and adalimumab to be effective in the treatment of PASH syndrome [1, 13-16]. Adalimumab has been successfully used in renal failure and found not to worsen renal function, even in the setting of hemodialysis [17]. The patient responded remarkably well to adalimumab and had complete remission of his PG lesions and achieved HiSCR within 8 weeks. Anakinra, an IL-1 receptor antagonist, is another treatment option that is showing great promise [5].

Table 3. *A summary of the published cases of PASH syndrome including this case.*

Case	Sex	Age at diagnosis	Comorbidities	BMI	Smoker	Gene mutation	Treatment	Response	Reference
1	M	48	None	NR	Yes	PSTPIP1	Topical and oral CS	Partial remission	Caldereron-Castrat et al 2016
2.	F	32	PCOS	39	No	-	CS, Dapsone, Rifampicin, Ciprofloxacin	Substantial improvement in PG.	Zivanovic et al 2016
3	M	24	Temporomandibular Joint Ankylosis	NR	NR	-	Systemic CS, Doxycyl-cine, amoxicillin/clavulin acid.	Improvement of PG	Wargo et al 2016
4	F	22	None	36.7	No	-	Infliximab, cyclosporine, dapsone	Complete remission	Staub et al 2015
5.	F	26	Ulcerative colitis with collectomy	NR	No	-	Adalumimab	Partial remission	Murphy et al 2015
6	M	23	None	NR	Yes	-	NR	NR	Duchatelet et al 2015
7	M	37	None	NR	Yes	-	NR	NR	Duchatelet et al 2015
8	F	29	None	NR	No	NCSTN	NR	NR	Duchatelet et al 2015
9	F	45	Cervicobrachial pain	NR	NR	MEFV NOD2	Infliximab	Partial remission	Marzano et al 2014
10	M	23	Crohn disease	NR	NR	-	Adalumimab	Complete remission	Marzano et al 2014
11	M	43	Spondyloarthritis	NR	NR	PSMB8	Infliximab	Partial remission	Marzano et al 2014
12	M	34	None	31.1	Yes	-	Isotretinoin, anakinra, ciclosporin	Partial remission	Braun-Falco et al 2012
13	M	44	None	33.8	Yes	-	Topical tacrolimus, oral CS, azathioprine	Partial remission	Braun-Falco et al 2012
14	M	33	Spondyloarthritis	NR	NR	-	Infliximab, isoniazid	Partial remission	Bruzzese et al 2012
15	M	34	Bariatric surgery	>40	NR	-	Infliximab	Partial remission	Marzano et al 2012
16	M	42	Chronic Renal Failure	>40	No	-	Adalumimab	Complete remission	Current Case

CS, corticosteroids; NR, Not Reported;

Conclusion

This case highlights the challenges associated with the treatment of PASH syndrome and affirms the use of adalimumab as an effective treatment option. ESRD may be a contributing factor in the development of PASH syndrome but this association needs further investigation. Our case supports the hypothesis that PASH syndrome may not be a monogenic disease but rather a disease with genetic heterogeneity.

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