CASE SERIES

Hidradenitis Suppurativa: a lesser-known cause of AA amyloidosis

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Abstract

Background: Hidradenitis suppurativa (HS) is a chronic, disabling skin disease. The estimated prevalence is 1-4 % worldwide. HS is a systemic inflammatory disease and can cause AA amyloidosis. The first report of HS-related amyloidosis dates back to 1966; since then, sporadic cases have been reported. Our work will be the first case series on HS and AA amyloidosis.

Case series: We report eight HS cases complicated with amyloidosis. Six patients were male. The median age was 44 years, and the median disease duration before the amyloidosis diagnosis was 15.5 years. In a mean follow-up of 18 ± 6 months, we achieved favorable renal responses in four of the eight cases (50 %). All cases had a dermatologic response, with four complete and four partial remissions.

Conclusion: HS is a systemic inflammatory disorder that may cause AA amyloidosis. Aggressive treatment of HS may halt the progression of amyloidosis. HIPPOKRATIA 2020, 24(1): 33-37.

Keywords: Hidradenitis suppurativa, AA amyloidosis, amyloidosis, end-stage renal disease

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Introduction

Hidradenitis suppurativa (HS) is a chronic, disabling disease characterized by deep-seated nodules, sinuses, and fibrosis in apocrine areas. The global prevalence of HS is variable and ranges from less than 1 % to 4 %[1]. The United States data suggests an incidence of 11.4 per 100,000 population. A specially designed study to diagnose under-diagnosed patients from the UK reported the prevalence to be 0.77-1.19 %[2,3].

The initial symptoms of HS can commence at any time between puberty and the fourth decade of life. Typically diagnosed in the second or third decades of life, HS is not anticipated to occur before a child turns ten. Females are two to four times more likely to develop HS than males[3]. The fact that African Americans have an unexpectedly high prevalence of HS highlights the importance of race or ethnicity in the onset of HS[4]. HS is also associated with smoking, obesity, bacterial infection, androgenic hormones, and chronic inflammatory diseases[5].

HS is a systemic inflammatory disease that may affect the kidneys. The oldest reference on renal involvement in HS dates back to the year 1966 when Moschella et al reported autopsy findings of a case of severe HS, AA amyloidosis, and pyelonephritis[6]. After that, HS cases complicated with AA amyloidosis have rarely been reported[7].

All chronic inflammatory diseases could result in AA amyloidosis if the disease activity is not controlled. Hence, a complete suppression of inflammation is critical for preventing amyloidosis[8]. This phenomenon underlies the importance of early diagnosis. Here we present our experience with eight HS patients with amyloidosis.

We staged all patients according to Hurley's staging system[9], a system that classifies HS patients into three categories based on disease severity: approximately 68 % of patients are categorized as stage 1, 28 % stage 2, and 4 % stage 3[10]. A clear or minimal state on physician global assessment for hidradenitis suppurativa scale is defined as a complete response, while a mild or moderate disease state means partial remission[11]. Both systems are detailed in Table 1.

Case Series

Case 1

A fifty-year-old male patient presented with severe HS (Hurley stage III) affecting, predominantly, the but-

Table 1: The Hurley staging system and the physician global assessment for hidradenitis suppurativa scale.

Hurley Stage	**Definition**
Stage I	Solitary or multiple isolated abscess formation without scarring and any sinus tract formation
Stage II	Recurrent abscess, single or multiple widely separated lesions with the formation of sinus tracts and cicatrization
Stage III	Diffuse and broad involvement across a regional area with multiple interconnected sinus tracts and abscess

PGA-HS	**Criteria**			
	Abscess	**Fistula**	**Inflammatory nodules**	**Non-inflammatory nodules**
Clear	0	0	0	0
Minimal	0	0	0	Some present
Mild	0	0	1-4	-
	Total: 1		0	-
Moderate	0	0	≥5	-
	Total: 1		≥1	-
	Total: 2-5		<10	-
Severe	Total: 2-5		≥10	-
Very severe	>5		-	-

tocks and groin, Familial Mediterranean Fever (FMF), and mild proteinuria (urinary protein excretion: 1.2 g/day). Although he was also suffering from hypoalbuminemia, the renal function was normal. He was suffering from HS and FMS for the preceding 20 years. A renal biopsy revealed AA amyloidosis. Adalimumab (ADA), anakinra, and infliximab (IFX) were administered. ADA ameliorated HS but not FMF, and anakinra ameliorated FMF but not HS. IFX resulted in partial suppression of HS activity and remission of FMF-related arthritis. The proteinuria decreased, albumin increased, and the renal function remained stable.

Case 2

A thirty-nine-year-old female with severe HS involving the axillae and groin was consulted for unexplained end-stage renal disease (ESRD). Ten months before our evaluation, she was diagnosed with kidney disease and administered ADA for HS. She was put on hemodialysis (HD) three months before. A bone marrow biopsy for severe anemia revealed AA amyloidosis infiltration. She responded well to ADA with no signs of active disease. However, the renal function did not recover. Anemia dramatically improved.

Case 3

A forty-four-year-old male with moderate to severe, widespread HS for 18 years was referred from the dermatology department for proteinuria. He had no comorbidities. He had been on ADA for a year. His urinary protein excretion, creatinine level, and albumin level were 7.2 g/day, 0.85 mg/dL, and 2.85 g/dL, respectively. A kidney biopsy was consistent with AA amyloidosis. He was allergic to IFX and anakinra, so ADA was continued. After 18 months of follow-up, his creatinine level was reduced to 4.85 mg/dL. He still excreted 11 g/day proteins in the urine, and his albumin level was 2.6 g/dL.

Case 4

A sixty-two-year-old male with moderate HS involving axillae with frequent exacerbations was consulted for elevated creatinine levels (4.12 mg/dL, baseline unknown) and mild proteinuria (1.6 g/day). He received topical and systemic antibiotics for HS. The disease duration was 30 years. A gastric biopsy revealed AA amyloidosis. Soon after the biopsy, he developed acute kidney injury due to over-the-counter painkillers. His creatinine level rose to 6.78 mg/dL, and hypervolemia necessitated HD. However, his creatinine level decreased to 3.3 mg/dL after two doses of IFX, and he no longer needed HD. During the treatment, he experienced macroscopic hematuria and was subsequently diagnosed with early-stage bladder cancer. The cancer was managed locally, and IFX therapy is being continued with close cancer surveillance.

Case 5

A forty-three-year-old male with severe HS of the axillae, buttocks, and groin had a creatinine level of 5.52 mg/dL, albumin level of 0.8 g/dL, and urinary protein excretion of 17 g/day, indicating proteinuria. A renal biopsy revealed AA amyloidosis. This case was also published elsewhere[12]. He responded well to IFX and had no activation of HS during 60 months of follow-up.

Case 6

A sixty-five-year-old male patient with severe widespread HS was consulted for ESRD. His creatinine level, albumin, and urinary protein excretion were 5.79 mg/dL, 1.9 g/dL, and 8 g/day, respectively. A rectal biopsy confirmed AA amyloidosis. He was a biologic-naïve patient, so ADA was started, which was followed by routine HD. During the 13 months of follow-up, no renal function recovery was observed; however, a partial dermatologic response was witnessed.

Case 7

A forty-three-year-old female was suffering from severe, widespread HS for 16 years. She was consulted for lower extremity edema. She had a urinary protein excretion of 12 g/day (proteinuria). Her creatinine and albu-

min levels were 0.64 mg/dL and 2.43 g/dL, respectively. She had no comorbidities and was on IFX for 14 months. A renal biopsy was consistent with AA amyloidosis. A switch from IFX to ADA resulted in a partial dermatologic response and over 50 % reduction in urinary protein excretion after eight months. Lower extremity edema also subsided.

Case 8

A 36-year-old male patient was consulted for proteinuria. He had Hurley stage II HS in addition to Crohn's disease for seven years. Both the conditions were diagnosed concomitantly, and relapsed while he was administered methotrexate, azathioprine, and glucocorticoids (GC). He was placed on etanercept (ET) three years ago. ET remitted Crohn's disease but not HS. His creatinine level, urinary protein excretion, and albumin were 0.79 mg/dL, 6 g/day, and 3.2 g/dL, respectively. A renal biopsy confirmed AA amyloidosis. Although after switching to ADA, the patient maintained his Crohn's disease state, HS activity was wholly abolished, and urinary protein excretion was reduced to 0.8 g/day. The patient is now stable under ADA for five months.

All the patients except two were males. The median age was 44, and the median disease duration before the diagnosis of AA was 15.5 years. In a mean follow-up of 18 ± 6 months, we achieved favorable renal responses in four of the eight cases (50 %). All the cases had a dermatologic response, with four complete and four partial remissions. The patients' baseline characteristics and follow-up data are presented in Table 2 and Table 3, respectively.

Discussion

We report eight cases of HS complicated with amyloidosis. Although the relationship between HS and amyloidosis was speculated in the 1960s when the first such case emerged, a recent cross-sectional study has confirmed a link between HS and amyloidosis[13]. The authors reported an increased risk of amyloidosis in patients with HS (Odds ratio =17.5; 95 % CI: 3.6-84.4; p <0.001)[13]. AA amyloidosis usually occurs with chronic inflammation. Uncontrolled inflammation leads to the overproduction of the serum amyloid A (SAA) protein. Insufficient clearance of AA protein results in its accumulation in tissues and fibril formation. The kidneys and gastrointestinal system are the most common deposition sites. The renal presentation may vary from asymptomatic proteinuria to nephrotic syndrome, with the former being more common during the early phases of deposition[8].

We believe that both FMF and HS contributed to amyloidosis in case 1. In a retrospective study conducted at the French FMF reference center, six of 151 (4 %) FMF patients were also found to have HS[14]. One of these six patients had AA amyloidosis with nephrotic syndrome and received anakinra. As a result of anakinra treatment, his FMF attacks subsided, and HS did not worsen. In a recent case-control study, Vural et al demonstrated that the patients with Hurley stage III HS were 4.17 times more likely to carry a pathogenic FMF gene variant as compared with patients with Hurley stage I and II[15]. This study strongly supported the involvement of the FMF gene in severe HS.

Anti-tumor necrosis factor (TNF) agents are indicat-

Table 2: Baseline characteristics and failed treatments of the reported eight patients with hidradenitis suppurativa complicated with amyloidosis.

Patient	Age/Gender	Smoking Status	Comorbidities	Duration of HS	Hurley Stage	Previous Treatments
1	50/M	Former	FMF + arthritis	20	3	Colchicine + Ab + Surgery + NSAII + GC + Dapson + Apremilast
2	39/F	Former	-	11	3	Ab + acitresin + isotretinoin + GC + surgery +ADA
3	44/M	Active	-	18	2-3	Ab + acitresin + surgery +ADA
4	62/M	Active	Hepatitis B COPD	30	1-2	Ab + GC
5	43/M	Active	-	15	2-3	Ab + GC + Surgery
6	65/M	Former	DM, CAD	10	3	Ab + isotretinoin + GC + surgery
7	44/F	Active	-	16	3	Ab + acitresin + isotretinoin + GC + surgery + IFX
8	35/M	Never	Crohn	7	2-3	Ab + GC + MTX + Aza + ET

M: male, F: female, Ab: systemic antibiotics, FMF: Familial Mediterranean Fever, COPD: chronic obstructive pulmonary disease, DM: diabetes, CAD: coronary artery disease, ADA: adalimumab, GC: glucocorticoid, iGC: intralesional glucocorticoids, IFX: Infliximab, MTX: methotrexate, Aza: azathioprine, ET: etanercept.

Table 3: Follow-up of the reported eight patients with hHidradenitis suppurativa complicated with amyloidosis.

Patient	Laboratory results at presentation	Biopsy site	Follow up (months)	Intervention	Current Status	HS
1	Cre: 0.93 Alb: 2.47 Prot: 1.2	Kidney	46	ADA Anakinra **IFX + MTX**	Cre: 0.98 Prot: 0.5 Alb: 3.7 FMF and arthritis in remission	Partial Remission
2	Cre: 5.69 (predialysis) Alb: 2.33	Bone marrow	13	None (ADA continued)	ESRD Alb: 2.67	Complete Remission
3	Cre: 0.85 Alb: 2.8 Prot: 7.2	Kidney	24	ACE inhibitor Colchicine (ADA continued)	Cre: 4.85	Partial remission
4	Cre: 4.12-6.78 Alb: 2.4 Prot: 1.6	Gastric	9	IFX	HD discontinued Alb: 2.7 Cre: 3.8 Bladder cancer cured	Complete Remission
5	Cre: 1,35 Prot:17 Alb: 2.4	Kidney	60	IFX	Cre: 1.42 Alb: 4.07 Pro: 3	Complete Remission
6	Cre: 5.79 Prot: 8 Alb: 1.9	Rectum	13	ADA	ESRD Alb: 2.5	Partial remission
7	Cre: 0.65 Prot: 12 Alb: 2.43	Kidney	8	ADA	Cre: 0.62 Prot: 2.7 Alb: 3.3	Partial remission
8	Cre: 0.79 Prot: 6 Alb: 3.2	Kidney	4	ADA	Cre: 0.71 Prot: 0.8 Alb: 3.8	Complete Remission

Cre: creatinine, Alb: albumin, Prot: 24-hour proteinuria in grams, HD: hemodialysis, ADA: adalimumab, IFX: infliximab, MTX: methotrexate, CsA: cyclosporine, FMF: Familial Mediterranean Fever, ESRD: end-stage renal disease.

ed for severe HS, and ADA is the first line[16,17]. Anakinra is also an option for severe HS that failed TNF alpha inhibitors[17]. Various reports have shown beneficial effects of anakinra on FMF and AA amyloidosis[14,18,19]. Both the drugs, ADA and anakinra, failed to treat HS and FMF in case 1. IFX has similar efficacy as ADA in severe HS patients. FMF of case 1 patient was completely remitted; urinary protein excretion was reduced by more than 50 %, and albumin level increased. We managed to control the HS of buttocks with additional GC partially. Case 2 was diagnosed with AA amyloidosis while she was already suffering from HD. We did not expect any recovery in her renal function, so her treatment for HS was not changed. Case 3 was allergic to IFX and anakinra, and he quickly progressed to ESRD, although TNF-α inhibitors can be used while the patients are on HD[20]. Unfortunately, they were not helpful for cases 2 and 3 in a renal sense. These inhibitors did not help in improving the renal condition of case 2 and case 3. Case 4 was our only amyloidosis case with mild to moderate HS. The patient responded well to IFX, and his creatinine level decreased below pre-biopsy values. In the 60th month of the follow-up of case 5, who was under continuous treatment with IFX, creatinine level was found to be stable, urinary protein excretion decreased by more than 50 %, and albumin was over 4 mg/dL. Detailed investigation of case 5 is published elsewhere[12]. These observations highlight the sustained efficacy of IFX. Similar to case 2, case 6 had a loss of renal function beyond salvage. After tailoring his treatment, according to HS, we achieved a partial remission. Case 7 is tracking a similar course to Case 5, and we believe she will enjoy a similar benefit. Case 8 was our only patient with accompanying Crohn's disease (inflammatory bowel disease), which is also known for its association with HS[21]. A change in the TNF-α inhibitor resulted in an improvement in all three conditions: HS, AA amyloidosis, and Crohn's disease.

Conclusion

The present study is the first case series of eight patients with HS and AA amyloidosis and offers a detailed investigation of the cases with a mean follow-up of 18 ± 6 months. However, this study suffers from the usual limitations of a case series: retrospective nature and the absence of a control group. The typical approach for preventing AA amyloidosis is controlling inflammation. If this approach fails, early diagnosis of AA fibril deposition and proactive management of the underlying dis-

order may lower proteinuria and slow down the disease progression to ESRD. We propose screening of severe HS cases with microalbuminuria/proteinuria and establishing a low threshold for kidney biopsy to achieve the goal of early diagnosis.

Conflict of interest

Authors reveal no conflicts of interest.

References

1. Alikhan A, Lynch PJ, Eisen DB. Hidradenitis suppurativa: a comprehensive review. J Am Acad Dermatol. 2009; 60: 539-561; quiz 562-563.
2. Ingram JR, Jenkins-Jones S, Knipe DW, Morgan CLI, Cannings-John R, Piguet V. Population-based Clinical Practice Research Datalink study using algorithm modelling to identify the true burden of hidradenitis suppurativa. Br J Dermatol. 2018; 178: 917-924.
3. Garg A, Lavian J, Lin G, Strunk A, Alloo A. Incidence of hidradenitis suppurativa in the United States: A sex- and age-adjusted population analysis. J Am Acad Dermatol. 2017; 77: 118-122.
4. Garg A, Wertenteil S, Baltz R, Strunk A, Finelt N. Prevalence Estimates for Hidradenitis Suppurativa among Children and Adolescents in the United States: A Gender- and Age-Adjusted Population Analysis. J Invest Dermatol. 2018; 138: 2152-2156.
5. Vekic DA, Frew J, Cains GD. Hidradenitis suppurativa, a review of pathogenesis, associations and management. Part 1. Australas J Dermatol. 2018; 59: 267-277.
6. Moschella SL. Hidradenitis suppurativa. Complications resulting in death. JAMA. 1966; 198: 201-203.
7. Iannone M, Oranges T, Chiricozzi A, De Tata V, Romanelli M, Dini V. Potential role of serum amyloid A in hidradenitis suppurativa. JAAD Case Rep. 2019; 5: 406-409.
8. Westermark GT, Fändrich M, Westermark P. AA amyloidosis: pathogenesis and targeted therapy. Annu Rev Pathol. 2015; 10: 321-344.
9. Hurley H. Axillary hyperhidrosis, apocrine bromhidrosis, hidradenitis suppurativa, and familial benign pemphigus: surgical approach. Roenigk RK, Roenigk HH (eds). Dermatologic surgery. Marcel Dekker, New York, 1989, 729-739.
10. Canoui-Poitrine F, Revuz JE, Wolkenstein P, Viallette C, Gabison G, Pouget F, et al. Clinical characteristics of a series of 302 French patients with hidradenitis suppurativa, with an analysis of factors associated with disease severity. J Am Acad Dermatol. 2009; 61: 51-57.
11. Kimball AB, Kerdel F, Adams D, Mrowietz U, Gelfand JM, Gniadecki R, et al. Adalimumab for the treatment of moderate to severe Hidradenitis suppurativa: a parallel randomized trial. Ann Intern Med. 2012; 157: 846-855.
12. Özer İ, Karaçin C, Adışen E, Güz G, Ali Gürer M. Two diseases one remedy? Systemic amyloidosis secondary to hidradenitis suppurativa: Treatment with infliximab. Dermatol Ther. 2017; 30.
13. Kridin K, Amber KT, Comaneshter D, Cohen AD. Amyloidosis in hidradenitis suppurativa: a cross-sectional study and review of the literature. Clin Exp Dermatol. 2020; 45: 565-571.
14. Abbara S, Georgin-Lavialle S, Stankovic Stojanovic K, Bachmeyer C, Senet P, Buob D, et al. Association of hidradenitis suppurativa and familial Mediterranean fever: A case series of 6 patients. Joint Bone Spine. 2017; 84: 159-162.
15. Vural S, Gündoğdu M, Gökpınar İli E, Durmaz CD, Vural A, Steinmüller-Magin L, et al. Association of pyrin mutations and autoinflammation with complex phenotype hidradenitis suppurativa: a case-control study. Br J Dermatol. 2019; 180: 1459-1467.
16. Gulliver W, Zouboulis CC, Prens E, Jemec GB, Tzellos T. Evidence-based approach to the treatment of hidradenitis suppurativa/acne inversa, based on the European guidelines for hidradenitis suppurativa. Rev Endocr Metab Disord. 2016; 17: 343-351.
17. Magalhães RF, Rivitti-Machado MC, Duarte GV, Souto R, Nunes DH, Chaves M, et al. Consensus on the treatment of hidradenitis suppurativa - Brazilian Society of Dermatology. An Bras Dermatol. 2019; 94: 7-19.
18. Varan Ö, Kucuk H, Babaoglu H, Guven SC, Ozturk MA, Haznedaroglu S, et al. Efficacy and safety of interleukin-1 inhibitors in familial Mediterranean fever patients complicated with amyloidosis. Mod Rheumatol. 2019; 29: 363-366.
19. Sevillano ÁM, Hernandez E, Gonzalez E, Mateo I, Gutierrez E, Morales E, et al. Anakinra induces complete remission of nephrotic syndrome in a patient with familial mediterranean fever and amyloidosis. Nefrologia. 2016; 36: 63-66.
20. De Wet J, Jordaan HF, Kannenberg SM, Tod B, Glanzmann B, Visser WI. Pyoderma gangrenosum, acne, and suppurative hidradenitis syndrome in end-stage renal disease successfully treated with adalimumab. Dermatol Online J. 2017; 23:13030/qt82d4m2zw.
21. Sattianayagam PT, Gillmore JD, Pinney JH, Gibbs SD, Wechalekar AD, Gilbertson JA, et al. Inflammatory bowel disease and systemic AA amyloidosis. Dig Dis Sci. 2013; 58: 1689-1697.