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Prevalence of antinuclear antibodies in hidradenitis suppurativa

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Abstract

Aim—The purpose of this study was to investigate the prevalence of antinuclear antibody (ANA) positivity in a cohort of patients with hidradenitis suppurativa (HS), and to assess the frequency of seroconversion during treatment with tumor necrosis factor (TNF)-α inhibitor therapy.

Methods—This prospective study was conducted through the Wound Etiology and Healing (WE-HEAL) Study. Immunofluorescence ANA testing was performed at baseline, and repeated when clinically indicated. ANA titers of ≥1:160 were considered positive. Data were collected on demographics and disease activity scores including the Hurley stage, the HS Sartorius score (HSS) and the active nodule (AN) count.

Results—At the time of data lock, 73 patients with a confirmed diagnosis of HS were enrolled, and four (5.4%) had baseline positive ANA. None of the patients had clinical evidence of systemic lupus erythematosus or other autoimmune diseases. There were no significant differences in demographics, baseline HSS (43.25 ± 47.55 compared to 59.48 ± 56.67, $P = 0.58$) or AN count (3.25 ± 3.20 compared to 3.45 ± 2.36, $P = 0.87$) in the ANA positive group. Of the 69 patients who were ANA negative at enrollment, 31 (45%) received TNF-α inhibitor therapy. During follow up, one patient developed drug-induced lupus secondary to TNF-α inhibitor use. Additionally, one patient seroconverted to ANA positive without sequelae and one patient developed drug-induced hepatitis secondary to TNF-α inhibitor use.

Conclusion—The prevalence of baseline ANA positivity in this HS population was similar to that seen in the general population (5.4%). The rate of seroconversion and drug-induced complications in this population were low.

Keywords

hidradenitis suppurativa; tumor necrosis factor-alpha; IL12/23; ANA; antinuclear antibody

Introduction

Hidradenitis suppurativa (HS) is a chronic, inflammatory disease of the apocrine sweat glands, characterized by recurrent abscessing inflammation.[1] While the pathogenesis of

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inflammation in HS is not well understood, studies suggest there may be an immunologic driver of the inflammatory response in this disease.[2–4]

Recent clinical trials have demonstrated efficacy of tumor necrosis factor-α (TNF-α) inhibitors in HS,[5,6] and rheumatologists are frequently consulted to assist with prescribing these agents for patients with HS. TNF-α inhibitors are known to trigger immunogenicity with induction of autoantibodies,[7,8] and in some cases drug-induced lupus.[9,10]

Antinuclear antibodies (ANA) are antibodies against nuclear antigens. They may be detected in patients with rheumatic disease, and they may also be triggered by drug exposures, malignancy and chronic infections. Additionally, ANA may be detected in subjects with no definable illness. Although a variety of detection methods are available for ANA testing, the most widely accepted technique is the use of immunofluorescent microscopy on human epithelial-2 (HEp-2) cells.[11] It is well recognized that healthy subjects may have a positive ANA at low titer; however, a titer of 1:160 exceeds the level seen in 95% of healthy subjects and is considered significant.

TNF-α inhibitors induce ANA in 11% to 70% of patients with rheumatoid arthritis depending on the agent used.[7,8] While the development of drug-induced lupus is relatively rare, there are also reports of other autoimmune reactions, including vasculitis, uveitis, demyelination and hepatitis.[12,13] One of the concerns from physicians using TNF-α inhibitors to treat HS is the risk of inducing a positive ANA.

Until now, the prevalence of ANA positivity in the HS population has not been evaluated, and the frequency of ANA induction in response to TNF-α inhibitors in HS has not been assessed. The purpose of this study was to investigate the prevalence of ANA positivity at baseline in a diverse cohort of patients with HS. A secondary goal was to investigate the frequency of seroconversion during follow up in this population.

METHODS

This research was conducted through the Wound Etiology and Healing Study (WE-HEAL Study), a biospecimen and data repository approved by The George Washington University Institutional Review Board (IRB 041408, NCT 01352078). The WE-HEAL Study is conducted in accordance with applicable regulations and guidelines governing clinical study conduct and ethical principles of human subjects research that have their origin in the Declaration of Helsinki. This is a longitudinal observational study. All subjects gave written informed consent for longitudinal collection of their data while they received treatment according to standard of care.

Inclusion criteria

This study was conducted utilizing data from the WE-HEAL subjects who had a confirmed diagnosis of HS. Diagnosis of HS was based on the Dessau Definition (Table 1). Time of data lock was 1 July, 2017

Data management

Longitudinal clinical data were abstracted from the electronic health record (EHR) and stored using Research Electronic Data Capture (REDCap), a secure, web-based application designed to support data capture in research studies.[14]

Clinical outcome measures

Clinical evaluation scores were completed by trained investigators at baseline and each subsequent visit.[15]

1. Hurley Stage—The Hurley Staging system (Table 2) was used to assess overall HS disease severity. In this staging system, lesions with single or multiple abscesses without sinus tracts or scaring are classified as stage I, lesions with recurrent abscesses with sinus tract formation and scarring are classified as stage II and lesions with diffuse involvement and multiple interconnected sinus tracts are classified as stage III.[16]

2. Active nodule count—The total number of abscesses and inflammatory nodules, known as the active nodule (AN) count was assessed at each visit.[17,18]

3. Modified Hidradenitis Sartorius Score—The modified Hidradenitis Sartorius Score (HSS) was used to assess disease activity.[19] This scoring system has been validated as a measure of disease activity in both longitudinal and intervention studies in HS.[6,15] A score of three points is assigned for each anatomic region involved; in each region, the presence of nodules scores one point and fistulae six points; the longest distance between lesions or size of the lesion is scored categorically to <5 cm (one point), 5–10 cm (three points) and > 10cm (nine points); finally, an assessment of whether each lesion is Hurley Stage III (nine points) or not (zero points) is made. Regional scores are summed to achieve a total modified HSS disease activity score. The upper limit of the scale is open.

ANA testing

ANA detection was performed by indirect immunofluorescence on HEp-2 cells through a commercial laboratory (Laboratory Corporation of America, Burlington, NC, USA). For this study, an ANA titer of 1:160 was designated as the cutoff for ANA positivity.

Statistical analysis

Data were analyzed using GraphPad Prism 5.03 (GraphPad Software, La Jolla, CA, USA). Differences in baseline demographics and in HS disease activity stratified by ANA status were examined using Student's *t*-test, Fisher's exact tests and Chi-squared tests as appropriate.

RESULTS

Baseline demographics

Of the 73 HS patients, four (5.5%) tested ANA positive at enrollment. There were no significant differences in age between the HS cohort who were ANA positive compared to those who were ANA negative (mean age 45.14 *vs.* 39.16 years, $P = 0.36$). However, the

mean (standard deviation) disease duration at enrollment was 21 (20.66) years in the ANA positive group compared to 9.92 (9.11) years in the ANA negative group ($P = 0.056$). There were no significant differences in the ANA positive compared to the ANA negative groups in terms of gender, race, smoking exposures or body mass index (Table 3).

Baseline disease activity in the ANA positive and negative groups

There were no significant differences in the numbers of patients who had Hurley stage III disease at enrollment in the ANA positive and negative groups ($P = 1.00$). Disease activity as measured by HSS was similar in both groups (43.25 [47.55] *vs.* 59.48 [56.67], $P = 0.58$), and the mean active nodule count at enrollment was also similar in both groups (3.25 [3.20] *vs.* 3.45 [2.36], $P = 0.87$)

Longitudinal ANA seroconversion in response to TNF-α inhibitors in HS

None of the patients who were ANA positive with a titer ≥1:160 at baseline were treated with TNF-α inhibitors. Of the 69 patients who were ANA negative at enrollment, 31 (45%) received TNF-α inhibitor therapy. Mean duration of therapy was 0.95 (range 0.05–2.99) years. Two of these patients seroconverted from ANA negative to ANA positive (based on the 1:160 titer cut-off) during follow up. Only one of these patients had evidence of drug-induced lupus. This patient developed arthritis, oral ulcers and skin rash after 20 months of infliximab (Remicade®) therapy and this syndrome resolved when the TNF-α inhibitor therapy was discontinued. This patient's HS has since gone into remission with ustekinumab (Stelara®) therapy. The other patient had complete remission of HS with infliximab (Remicade®) therapy, and discontinued treatment after 20 months in order to travel to a tuberculosis endemic area. The positive ANA was noted upon his return but the patient was asymptomatic. The patient's HS remained in remission and TNF-α inhibitor was not restarted. One other patient treated with TNF-α inhibitor therapy developed drug-induced hepatitis with positive anti-actin (smooth muscle) antibody. In this patient, the TNF-α inhibitor therapy was discontinued and the patient was switched to ustekinumab.

DISCUSSION

Approximately 5% of otherwise healthy individuals have a positive ANA at a titer of 1:160.[11] ANA positivity is more common in women than men, and is more common in African Americans than Caucasians. Since HS in the USA has a higher prevalence in women and African Americans, there is a rational reason to be concerned that this population might have a higher prevalence of ANA positivity than the general population. The WE-HEAL cohort reported here has a demographic profile representative of the HS population in the USA (more than 70% female and more than 70% African American) and in this study we did not find a higher than expected frequency of ANA positivity.

Although the number of patients with a positive ANA at baseline in this study was small, the HS patients who were ANA positive did not have significant differences in age, sex, race or disease activity compared to ANA negative patients. However, the patients who were ANA positive at enrollment had a slightly longer duration of disease compared to the ANA negative group. This finding did not reach statistical significance due to the small sample

size. However, it is possible that prolonged HS itself over and above medication exposures increases the risk of autoantibody formation. This observation merits further investigation in a larger study.

In the longitudinal follow up of the WE-HEAL cohort reported here, only two patients developed ANA seroconversion with TNF-α inhibitor therapy. Since this is a longitudinal study, one limitation of this data is that subjects who had been commenced on TNF-α inhibitor therapy recently, did not have extensive follow up. However, the seroconversion rate of 6.5% is consistent with the frequency of ANA seroconversion seen in patients with other autoimmune diseases treated with TNF-α inhibitor therapy.[7,8] Studies investigating the frequency of ANA seroconversion in patients with other autoimmune diseases treated with infliximab, etanercept and adalimumab indicate rates of 29–77%, 11–36% and 13%, respectively.[7,8] In comparison, the rates seen in our study were lower, indicating that TNF-α inhibitor therapy in HS carries no greater risk for inducing autoimmunity than in other diseases such as rheumatoid arthritis.

CONCLUSION

The WE-HEAL study is a longitudinal observational study of a diverse population of patients with either chronic wounds or HS. The prevalence of baseline ANA positivity in the WE-HEAL HS population was similar to that seen in the general population. While there is a known risk of development of ANA positivity and drug-induced lupus with TNF-α inhibitor use, we did not see a high rate of seroconversion or drug-induced complications in this cohort.

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Table 1

Dessau Criteria for diagnosis of HS: 1st International Conference on HS, 2006, Dessau, Germany[20–22]

Criteria	Details
Presence of recurrent painful or suppurating nodules	Present on two or more occasions within 6 months
Involvement of typical anatomic regions:	Axilla Genitofemoral area Perineum Gluteal area Inframammary area
Typical lesions	Nodules (inflamed or non-inflamed) Sinus tracts (inflamed or non-inflamed) Abscesses Scarring
Secondary criteria	Family history of HS

HS, hidradenitis suppurativa

Table 2

Hurley staging system

Stage	
0	No active HS
I	Localized abscess, no sinus tracts
II	Recurrent abscesses with sinus tracts and scarring, single or multiple widely separated lesions
III	Diffuse involvement with multiple interconnected sinus tracts and abscesses
NA	Post-operative patient in whom Hurley score cannot be assessed either due to wound, wound vacuum-assisted closure or integra placement.

HS, hidradenitis suppurativa

Table 3

Baseline demographics and disease activity scores in the HS patients who were ANA positive and negative at baseline

	ANA positive (*n* = 4)	**ANA negative (*n* = 69)**	***P*-value**
Mean age, years (SD)	45.14 (16.2)	39.16 (12.59)	0.36
Female sex, number (%)	3 (75%)	49 (71%)	1.00
African American race, number (%)	3 (75%)	50 (72.5%)	1.00
Current or ever smokers, number (%)	2 (50%)	33 (47.8%)	1.00
Mean body mass index, kg/m^2 (SD)	34.70 (7.50)	33.99 (6.76)	0.84
Mean pain score at enrollment (SD)	2.33 (4.04)	2.79 (3.25)	0.82
Mean disease duration at enrollment (SD)	21 (20.66)	9.92 (9.11)	0.056
Hurley stage III at enrollment, number (%)	2 (50%)	34 (49.3%)	1.00
Mean modified Hidradenitis Sartorius score at enrollment (SD)	43.25 (47.55)	59.48 (56.67)	0.58
Mean active nodule count at enrollment	3.25 (3.20)	3.45 (2.36)	0.87

HS, hidradenitis suppurativa; ANA, antinuclear antibodies