ONLINE FIRST

Hidradenitis Suppurativa

The Role of Deficient Cutaneous Innate Immunity

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Objective: To evaluate the expression of innate immunity markers at the site of nodules caused by hidradenitis suppurativa (HS).

Design: Prospective analysis of 12 patients with HS.

Setting: Unité de Cancéro-Dermatologie, Nantes Hospital, Nantes; Service de Dermatologie, Poitiers Hospital, Poitiers; and Service de Dermatologie, Clinique de Courlancy, Reims, France

Patients: Twelve patients (Hurley stage I or II) in whom the disease had progressed for at least 6 months and who had a minimum of 2 closed nodules in typical sites.

Main Outcome Measures: Two biopsies were performed at baseline: one in a closed inflammatory nodule and one in healthy adjoining skin. Patients were treated for 3 months with zinc gluconate at a dosage of 90 mg/d. A new biopsy was then performed in the same nodule. Innate immunity markers (toll-like receptors 2, 3, 4, 7, and 9; intercellular adhesion molecule 1; interleukin [IL] 6 and 10; tumor necrosis factor; α melanocyte stimulating hormone; transforming growth factor β; β-defensin 2 and 4; and insulinlike growth factor 1) were studied by immunohistochemical analysis.

Results: We observed significantly decreased expression ($P < .001$) of all the innate immunity markers studied except IL-10 in nonlesional and lesional HS skin. The downregulation of innate markers was significantly stronger in lesional HS skin compared with normal skin except for tumor necrosis factor. Three months of zinc treatment induced a significant increase in the expression of all the markers involved in innate immunity.

Conclusion: Our study demonstrates for the first time, to our knowledge, that a deficiency of the main innate immunity markers in typical HS sites may explain the development of chronic inflammatory nodules in this disease.

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HIDRADENITIS SUPPURATIVA (HS) is a skin disorder of unknown etiology and pathogenesis. Its prevalence is reported to range from 1:300 to 4:100 in the general population.[1] It is characterized by the development of nodular inflammatory lesions with a secondary evolution toward abscesses that are mainly localized near the apocrine glands. Recently, 4 mutations were identified in the gene coding for γ-secretase, a transmembrane protease composed of 4 essential protein subunits: 1 catalytic presenilin subunit and 3 cofactor subunits (presenilin enhancer 2, nicastrin, and anterior pharynx defective 1). The 4 mutations have been identified in the genes encoding presenilin 1 (1 deletion) and nicastrin.[2]

Current theories about HS pathogenesis implicate hyperkeratosis of the follicular epithelium as the hallmark pathogenetic process that leads to the occlusion of the apocrine glands with subsequent follicular rupture, inflammation, and a possible secondary infection by corynebacteria.[3] The clinical improvement that results from therapies targeting the tumor necrosis factor (TNF) agrees with this theory of inflammatory pathogenesis because TNF is a major proinflammatory cytokine. The innate immune system plays an important role because it is the first line of defense or the first barrier against foreign organisms and substances. It also plays a role in acute and chronic inflammation. The inflammatory response is a major component or barrier created as part of innate immunity. Therefore, it is highly probable

that skin affected by HS has abnormal innate immunity. The present study sought to evaluate the characteristics of various cutaneous innate immunity markers in skin that appeared to be clinically normal and in closed inflammatory nodules in patients with HS before and after 3 months of treatment with zinc gluconate.

METHODS

Biopsy specimens from 12 patients were obtained for this multicenter study before and after 3 months of treatment with zinc gluconate, 90 mg/d. Inclusion criteria were being 18 to 65 years old with stage I or II (Hurley classification[4]) HS that had evolved for at least 6 months and having at least 2 closed inflammatory nodules in typical areas of the disease, mainly, the suprapubic region, axillae, groin, and inframammary and gluteal folds. Patients who took zinc salts for more than 6 months were excluded, as well as patients who had received the following general treatments within the month before the biopsies: anti-inflammatory, systemic antibiotic, immunosuppressive agent, corticosteroid, isotretinoin, sulfonamide antibacterial, anti-TNF, dapsone, acitretin, colchicine, lithium salt, and topical antibiotic or corticosteroid treatments. All patients provided written informed consent, and the study was approved by the ethics committee of Pays de La Loire, France.

The main objective was to determine the expression level of different innate immunity markers in the epidermis of both normal and inflammatory skin (closed nodules) affected by HS, including toll-like receptors (TLRs) 2, 3, 4, 7, and 9; integrin intercellular adhesion molecule 1 (ICAM-1); the cytokines interleukin (IL) 6 and 10; TNF; α melanocyte stimulating hormone (α-MSH); transforming growth factor β (TGF-β); insulinlike growth factor 1 (IGF-1); and β-defensin 2 and 4. The secondary objective was to determine the modulation of innate immunity markers in inflammatory skin after 3 months of treatment with zinc gluconate, 90 mg/d.

For each patient, 2 biopsy specimens were taken before the treatment: one from a closed inflammatory lesion (lesional HS skin) and the other from nonlesional HS skin. At the end of zinc treatment, a new biopsy specimen was taken close to the site of the initially removed inflammatory lesion (lesional HS skin). Six biopsy specimens from the suprapubic region obtained from 6 different individuals matched for age and sex were used as control skin samples; these biopsy specimens were obtained during plastic surgery. Biopsy specimens from 2 inflammatory acne lesions, 2 folliculitis lesions, and 2 psoriatic lesions were also used as controls and were obtained from 6 different patients.

IMMUNOHISTOCHEMICAL ANALYSIS OF CUTANEOUS SECTIONS

Immunohistochemical analysis was performed using the streptavidin/peroxidase technique as previously described.[5] Formalin-fixed paraffin-embedded cutaneous sections were incubated overnight at 4°C with the primary antibody. Fourteen different monoclonal antibodies were used to explore innate immunity: anti–TLR-2, -3, -4, -7, and -9 (8 µg/mL each; all from Santa Cruz Biotechnology, Inc, Santa Cruz, California); anti–ICAM-1 (5 µg/mL; Beckman Coulter, Inc, Brea, California); anti-TNF (1/50; Diagnostic BioSystems, Pleasanton, California); anti–IL-6 (10 µg/mL; AbD Serotec, Oxford, England); anti–IL-10 (10 µg/mL; R&D Systems, Inc, Minneapolis, Minnesota); anti–TGF-β (10 µg/mL; AbD Serotec); anti–α-MSH (1/50; PROGEN Biotechnik GmbH, Heidelberg, Germany); anti–β-defensin 2 and 4 (β-defensin 2, 1/50, and β-defensin 4, 5 µg/mL; both from Abcam, San Francisco, California); and anti–IGF-1 (5 µg/mL; R&D Systems, Inc, Lille, France). Negative controls were obtained with a mouse monoclonal IgG1κ isotype control (DakoCytomation, Trappes, France). Immunohistochemistry slides were observed under a modular universal research microscope (Aristoplan; Leica Microsystems, Wetzlar, Germany), and photographs were taken with a digital single-lens reflex camera (D70S; Nikon, Inc, Melville, New York). The presence of staining was assessed within the epidermis. For each marker, the epidermal protein level on the slide was determined by the addition of 3 subscores for the basal layer, spinous layer, and granulose layer/stratum corneum. Each subscore was evaluated on a 5-point scale: null (0), very weak (1), weak (2), moderate (3), strong (4), and very strong (5). Thus, the maximum score for a slide was 15. Two different examiners (B.D. and A.-C.K.) viewed the slides in a blinded reading.

STATISTICAL ANALYSIS

For each immunity marker, the averaged values obtained for the controls were subtracted from the scores obtained for the inflammatory and noninflammatory areas at baseline and after 3 months of treatment. Differences in these scores were calculated for each patient. A mixed model, including 2 fixed factors (zone and investigator) and a random factor (subject), was designed to test the difference against 0 (comparison vs control) and to compare the results between inflammatory and noninflammatory zones at baseline and after 3 months of treatment. Spearman rank correlation coefficients were calculated to assess the agreement level of the examiner results for controls and patients. We used SAS statistical software (version 9.2 for Windows; SAS Institute, Inc, Cary, North Carolina) for all calculations.

RESULTS

PATIENTS

Twelve patients were included (mean [SD] age, 29.4 [8.4] years [median, 28.5 years; range, 19-42 years]); all were women. The mean (SD) illness duration was 10.1 (7.3) years (median, 9 years). Biopsy specimens were obtained from normal and inflammatory HS skin in the axillary, inframammary, and inguinal areas of 2, 1, and 9 patients, respectively.

IMMUNOHISTOCHEMICAL ANALYSIS

Scores obtained by each expert for each marker correlated well between the 2 groups (for controls, $r=0.933$; for patients, $r=0.930$). All results obtained before treatment are summarized in the **Table**.

Before treatment, the expression of all the markers examined was significantly suppressed in the epidermis of nonlesional HS skin compared with control skin (Table) except the expression of IL-10, which was significantly higher in nonlesional HS skin compared with control skin. Similar results were obtained for lesional HS skin compared with control skin (Table).

When compared with nonlesional HS skin, we observed that TLR-4, β-defensin 4, and IL-10 expression was significantly suppressed in lesional HS skin without any other statistically significant change for the other markers (Table). In the 6 inflammatory control skin

Table. Expression of Innate Immunity Markers in Nonlesional and Lesional HS Skin and in Lesional HS Skin After 3 Months of Zinc Treatment and in Control Skin

	Immunohistochemical Analysis Score, Mean (SD)			
		At Baseline		Lesional HS Skin After 3-mo Treatment With Zinc Gluconate (n=12)[c]
Innate Markers	Control Skin (n=6)	Nonlesional HS Skin (n=12)[a]	Lesional HS Skin (n=12)[b]	
TLR-4	1.60 (0.24)	1.06 (0.40)	0.74 (0.50)	1.20 (0.49)
P value		<.001	.007	<.001
β-Defensin 4	1.22 (0.38)	0.92 (0.38)	0.49 (0.37)	0.94 (0.50)
P value		<.001	.001	<.00
TLR-2	2.00 (0.00)	0.92 (0.49)	0.83 (0.42)	1.18 (0.50)
P value		<.001	>.99	<.001
ICAM-1	1.78 (0.33)	0.97 (0.44)	0.79 (0.34)	1.22 (0.56)
P value		<.001	.25	<.001
IL-6	0.65 (0.35)	0.39 (0.20)	0.29 (0.18)	0.63 (0.30)
P value		<.001	.21	<.001
TNF	0.85 (0.41)	0.53 (0.46)	0.35 (0.24)	0.80 (0.38)
P value		<.001	.08	<.001
α-MSH	2.18 (0.36)	0.92 (0.41)	0.74 (0.44)	1.06 (0.57)
P value		<.001	.13	<.001
TGF-β	0.40 (0.29)	0.25 (0.33)	0.17 (0.17)	0.31 (0.30)
P value		.001	.60	.07
TLR-3	0.82 (0.21)	0.43 (0.47)	0.38 (0.42)	0.55 (0.48)
P value		<.001	>.99	.06
TLR-7	1.71 (0.43)	0.83 (0.45)	0.60 (0.36)	1.09 (0.55)
P value		<.001	.15	<.001
TLR-9	1.04 (0.19)	0.56 (0.23)	0.43 (0.28)	0.69 (0.40)
P value		<.001	.40	.007
β-Defensin 2	2.13 (0.29)	1.07 (0.40)	1.09 (0.46)	1.21 (0.55)
P value		<.001	>.99	>.99
IGF-1	1.83 (0.00)	0.71 (0.39)	0.52 (0.33)	1.16 (0.56)
P value		<.001	.25	<.001
IL-10	0.15 (0.11)	0.97 (0.49)	0.65 (0.48)	1.07 (0.49)
P value		<.001	.03	.004

Abbreviations: HS, hidradenitis suppurativa; ICAM-1, intercellular adhesion molecule 1; IGF-1, insulinlike growth factor 1; IL, interleukin; α-MSH, α melanocyte stimulating hormone; TGF-β, transforming growth factor β; TLR, toll-like receptor; TNF, tumor necrosis factor.

[a] *P* values represent nonlesional HS skin at baseline vs control skin.

[b] *P* values represent lesional vs nonlesional HS skin at baseline.

[c] *P* values represent lesional HS skin after 3 months of zinc treatment vs lesional HS skin at baseline.

samples (acne, folliculitis, and psoriasis), expression of all the markers was increased compared with that in lesional and nonlesional HS skin (grade 3 or 4 on a 5-point scale) except for IL-10 (grade 1 on a 5-point scale) (data not shown). Finally, we observed that a 3-month zinc treatment induced significantly increased expression of all the key innate immunity markers in lesional HS skin except for TGF-β, β-defensin 2, and TLR-3 compared with lesional HS skin samples obtained before the treatment (Table).

COMMENT

This study demonstrates a significant decrease in expression of all the cutaneous innate immunity markers examined in lesional and nonlesional skin of HS patients compared with control skin except IL-10, which was increased in lesional and nonlesional HS skin compared with normal skin. This downregulation affects the TLRs, β-defensins, ICAM-1, and cytokines (IL-6, IGF-1, α-MSH, TGF-β, and TNF). In addition, TLR-4, β-defensin 4, and IL-10 expression was suppressed in lesional compared with nonlesional HS skin. These results suggest that a deficient cutaneous innate immunity may play a crucial role in the development of chronic inflammatory nodules in HS. Thus, the production of TLR-2, TLR-4, and β-defensin 2 and 4 by the keratinocytes in inflammatory nodules was not induced as expected during the activation of an innate immune response and as observed in our inflammatory skin biopsy specimens (acne, folliculitis, and psoriasis), confirming the results reported in the literature.[6,7] In addition, the proinflammatory cytokines IL-6 and TNF were not induced in the inflammatory nodules; instead, both were significantly decreased. Moreover, because defensins also have antiinfectious properties, a decrease in defensins may enable the development of anaerobic bacteria, such as corynebacteria, in apocrine sweat. Finally, ICAM-1, which is considered a marker of keratinocyte activation and the expression of which is induced by interferon gamma, was weakly expressed by the keratinocytes, confirming the abnormalities in the in situ inflammatory reaction.

Our results are similar to those obtained by Giamarellos-Bourboulis et al[8] in the blood. However, Matusiak et

al[9] demonstrated increased serum TNF concentration in HS patients compared with healthy controls. This result may be explained by the fact that plasma TNF levels do not reflect the status of innate immune activity as precisely as monocyte or keratinocyte levels. Recently, van der Zee et al[10] also reported that IL-1β, TNF, and IL-10 levels were significantly elevated in lesional and perilesional HS skin compared with healthy control skin and psoriatic skin, suggesting that the inflammation is strong in HS skin and providing a rationale for anti-TNF biotherapy in HS patients. These results were obtained using a method that is quite different from ours in which cytokine levels were measured in culture supernatants after skin biopsy specimens were incubated in a culture medium for 24 hours, raising the question of the nature of the cells producing these cytokines. Indeed, keratinocytes, as well as fibroblasts, monocytes, or lymphocytes, may be the source of such cytokines. These different results support the hypothesis of a disease affecting the cutaneous innate immunity. The nonactivation of the TLRs and β-defensins may prevent the activation of the keratinocytes and thus may also prevent the production of proinflammatory cytokines. In addition, the increased expression of cytokine IL-10 may downregulate the activation of the adaptive immunity. A reduced natural killer cell percentage over time and a lower monocyte response triggered by bacteria are observed in blood from HS patients.[7] Finally, Wolk et al[11] demonstrated recently that HS lesions are associated with deficient expression of IL-20 and IL-22 receptors and with increased expression of IL-22 binding protein, the natural IL-22 inhibitor.

A 3-month treatment with zinc gluconate, 90 mg/d, stimulated the innate immunity with significantly increased expression of all the markers examined except TGF-β, TLR-3, and β-defensin 2. Zinc salts act at different levels on innate immunity, resulting in polynuclear neutrophil chemotaxis and phagocytosis, natural killer cell activation,[12,13] integrin expression inhibition (ICAM-1 and leukocyte function–associated antigen 3) by keratinocytes in inflammatory diseases,[14] and TNF and IL-6 downregulation.[15] All these data, which demonstrate that zinc has anti-inflammatory activity, appear to completely contradict the results obtained in our study. However, the activity of trace elements has already been reported to be dose dependent. Indeed, in cell culture, very high zinc concentrations (>100μM) in a serum-free culture medium have been previously reported to stimulate the secretion of proinflammatory cytokines by the monocytes.[16] In addition, a variety of studies indicate that, depending on its concentration, zinc can be either proapoptotic or antiapoptotic, which confirms that it can have opposite effects depending on the dose.[17-20] Zinc gluconate might thus downregulate innate immunity at low doses and stimulate innate immunity at high doses.

Recently, γ-secretase, a mutated gene, has been identified in HS as an intramembranous cleavage mediator of various type I membrane proteins, including the amyloid precursor protein and Notch B.[21] Interestingly, γ-secretase genetic inactivation in mouse skin leads to epidermal and follicular abnormalities that are histopathologically similar to those observed in HS and arise through alterations in Notch signaling.[22] In addition, a new link between HS and zinc seems to be established. Indeed, zinc finger protein 64 has been identified as a coactivator of Notch1. Zinc finger protein 64 is associated with the intracellular domain of Notch1, is recruited to the promoters of Notch target genes *HES1* and *HEY1*, and transactivates them.

In conclusion, this study demonstrates for the first time, to our knowledge, that the deep chronic inflammation caused by HS may directly be related to deficient innate immunity in the skin. Some familial cases have been reported, suggesting that a mutation in the TLR or defensin genes may explain the lack of innate immunity in some patients. Several innate immunity markers, such as the TLRs, defensins, integrins, and proinflammatory cytokines, are downregulated and associated with increased production of the immunosuppressive cytokine IL-10, which thus may worsen the skin's deficient innate immunity. This strongly deficient innate immunity may explain the severity of the inflammatory lesions and the chronic evolution of the disease.

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Author Contributions: Dr Dréno had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design*: Dréno, Khammari, Moyse, and Blouin. *Acquisition of data*: Khammari, Brocard, Guillet, Léonard, and Knol. *Analysis and interpretation of data*: Dréno, Moyse, and Knol. *Drafting of the manuscript*: Dréno. *Critical revision of the manuscript for important intellectual content*: Khammari, Brocard, Moyse, Blouin, Guillet, Léonard, and Knol. *Statistical analysis*: Moyse. *Obtaining funding*: Dréno and Brocard. *Administrative, technical or material support*: Khammari, Brocard, Guillet, Léonard, and Knol. *Study supervision*: Dréno and Khammari.
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Announcement

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