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CONCISE COMMUNICATION

Mast cells in hidradenitis suppurativa: a clinicopathological study

Emil K. List[1,2] · Jose C. Pascual[3] · Kian Zarchi[1,2] · Birgit M. Nürnberg[2,4] · Gregor B. E. Jemec[1,2]

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Abstract

Mast cells (MC) have been observed in hidradenitis suppurativa (HS) lesions. Their potential role in the pathogenesis of HS is unknown. The aim of this study was to assess the number and distribution MC in HS lesions, and its association with disease and itch severity. We studied biopsies from HS-lesions and perilesional skin from 34 HS patients. The samples were stained with CD117 and toluidine blue, and the number of MC determined semi-quantitatively (40× magnification). The distribution of MC was also noted. The clinical features of the disease were extracted from patients' case records and a questionnaire-based database. MC were present to a greater degree in HS-lesions than in perilesional skin ($P=0.004$). Disease severity (Sartorius score) was correlated to with MC count and itch when adjusted for sex and age ($P=0.042$). Duration of the disease could not been significantly correlated with MC count. A positive correlation between MC count and HS activity was detected, suggesting a potential link between MC and HS.

Keywords Hidradenitis suppurativa · Mast cell · Itch · Pruritus

Abbreviations

HS	Hidradenitis suppurativa
QoL	Quality of life
MC	Mast cells
Ig	Immunoglobulin

Introduction

Hidradenitis suppurativa (HS) is characterized by recurring deep-seated nodules and abscesses accompanied by draining tunnels (sinus tracts) and bridged scars. The lesions are located in the intertriginous areas of the skin but ectopic lesions can occur [18]. In addition to pain and malodor, pruritus has been described as one of the key symptoms and negative influences on the quality of life (QoL) in HS [13, 20]. Microscopic examination of early HS-lesions shows hyperkeratinization of the follicular infundibulum, follicular plugging, dilated hair follicles, cyst formation, and an infiltration of neutrophils [2]. Later, multinucleated giant cells, monocytes, macrophages predominate in the inflammatory infiltrate. In addition, the epidermis can display a psoriasiform hyperplasia, which can also be observed in normal-appearing perilesional skin as well as in chronic lesions [19]. One of the hallmarks of cutaneous lesions in HS is the development of epithelialized fistulas that are exclusive to chronic lesions. Finally, the number of lymphocytes, tryptase-positive mast cells (MC), and CD20+ and CD79+ B cells and CD138+ plasma cells are also increased in HS [16]. However, the pathogenic role of MC in the evolution of HS-lesions it is not fully understood.

On the other hand, pruritus is a key symptom in HS; however, its pathogenesis in HS has been only partially elucidated [11]. In addition to the increased number of MC in early, chronic lesions and in normal-appearing perilesional skin, increased serum levels of immunoglobulin (Ig) E have been described in patients with moderate-to-severe HS [12]. Theoretically, this enhancement of IgE production and a dense infiltration of MC in HS could trigger de-granulation of these cells, releasing histamine and causing pruritus. However, the cause of pruritus in HS, could be multifactorial

✉ Jose C. Pascual
jcpascualramirez@hotmail.com

1 Department of Dermatology, Zealand University Hospital, Roskilde, Denmark

2 Health Sciences Faculty, University of Copenhagen, Copenhagen, Denmark

3 Department of Dermatology, Alicante University General Hospital, Alicante Institute for Health and Biomedical Research (ISABIAL-FISABIO Foundation), C/Maestro Alonso s/n. CP, 03010 Alicante, Spain

4 Department of Pathology, Zealand University Hospital, Roskilde, Denmark

including other mechanisms such as small-fiber neuropathy due to scar formation [3], or irritant contact dermatitis due to discharge of purulent material over the epidermis causing maceration.

Moreover, mediators secreted by MC such as histamine and tryptase, can diffuse through the dermal matrix and have been shown to induce increased keratinocyte activity including hyperkeratinization through the H1-receptor [1, 21]. Hyperkeratinization is a key feature of early HS, and keratinocytes are also involved in the formation of HS tunnels (sinus tracts) [4].

In addition, IL-17 is elevated in both skin and serum of HS patients [5, 7, 14]. It was previously thought that TH_{17} cells were the sole IL-17 producing cells; however, MC appear to be a significant source of IL-17 secretion and may play a major part in other auto-inflammatory diseases [6]. IL-17 orchestrates innate immune responses against extracellular pathogens by inducing expression of antimicrobial peptides and neutrophil-trophic chemokines [10]. Similarly, in psoriasis lesions an increased numbers of mast cells and neutrophils contribute to the release of pathogenic cytokine IL-17 through the formation of extracellular traps. [6] The anti-inflammatory cytokine IL-10 is also significantly elevated in HS lesions. Van der Zee et al. speculate that the source could be macrophages responding to lipopolysaccharides from microbes residing in HS lesions [17]. Moreover, non-IgE sensitized MC have been shown to induce expansion of IL 10-competent CD5 + B cells [9].

The aim of this study was to assess the number and distribution of MC in HS lesions, and its association with disease and itch severity.

Materials and methods

A retrospective cross-sectional study was designed to assess the number and distribution of MC in HS lesions. The association between MC count and distribution with disease severity, disease duration, and itch was also evaluated. All patients were scheduled for surgery of recalcitrant lesions, and none were treated with immunosuppressive therapy neither locally nor systemically for 2 weeks prior to surgery.

Skin biopsies and recorded medical data from 34 HS-patients from the Department of Dermatology, Roskilde Hospital, Copenhagen were reviewed. Tissue samples were obtained from surgical excisions or biopsies taken during CO_2 laser surgery. All samples were obtained between 2011 and 2014. In 21 out of 34 tissue samples both lesional and clinically uninvolved perilesional skin was available, and in 13 patients, only lesional skin was available. If the patient had multiple tissue samples due to several surgical procedures only the first biopsy was considered.

Mast cells

A combined qualitative and semi-quantitative approach was used. Two staining methods were used, CD117 and toluidine blue. Qualitatively, the distribution MC was classified either as perivascular, pilosebaceous or interstitial. For semi-quantitative analysis, a Board certified dermatopathologist (JCP) assessed the number of MC with CD117 and toluidine blue stain, respectively, in a representative area of each specimen at 40X magnification. Counting was duplicated as quality assurance in a subset of slides by an independent observer (BMN).

Disease severity assessment

Disease severity was assessed with Hurley and Sartorius scales [13, 15]. Both scores were extracted from the files of the patient as close as possible to the time of the biopsy (max. 6 month before). Itch was assessed throughout a questionnaire. Patients were asked to report the number of days with the itch from the lesional areas (range 0–31) and self-reported itch in a visual analog scale from 0 to 10, with 0 representing no itch and 10 being the worst itch they could imagine.

Statistical analysis

Categorical data are reported by frequency and percentage and continuous data by mean and standard deviation. The correlations between the numbers of MC measured by the CD117 method and Toluidine blue method and the number of MC in lesional and perilesional skin were determined by calculating the Spearman's correlation coefficient. Univariable and multivariable linear regression analyses were undertaken to investigate the association between the number of MC and the disease severity (Sartorius score), disease duration, degree of itching during the past week, and number of days with itching during the past month. In the multivariate model, the results were adjusted for age and sex; however, since the disease duration might impact patients' quality of life and number of MC in lesional skin was adjusted for age, sex and disease duration. P values < 0.05 were considered as significant. All analyses were performed in the statistical program R, version 2.15.2 (R Development Core Team, 2013).

Table 1 Demographic, clinical and pathologic findings

Variable	N = 34	
Age (years)	39.3 ± 9.8	
Female, no. (%)	29 (85.3)	
Disease duration (years)	18.7 ± 9.1	
Hurley II, no. (%)	30 (88.2)	
Sartorius score	30.7 ± 24.6	
Itch, last week (visual analog scale 0–10)	4.3 ± 3.2	
Days with itch during the last month, days	13.8 ± 11.9	
MC count lesion, CD117	27.8 ± 13.2	
MC count perilesional, CD117	16.6 ± 10.7	
MC count lesion, toluidine blue	15.7 ± 8.7	
MC count perilesional, toluidine blue	9.5 ± 7.2	
Pattern of distribution	Lesional skin ($n = 34$)	Perilesional ($n = 21$)
Pilosebaceous	6 (17.6)	2 (9.5)
Perivascular	7 (20.6)	9 (42.9)
Interstitial	21 (61.8)	10 (47.6)

Except where indicated otherwise, values are mean and standard deviation (SD)

MC Mast cells

Results

A total of 34 patients were included [29 (85.3%) females], with a mean age of 39.3 years (range: 22–64). Mean duration of the disease was 18.7 years. (Table 1.) Thirty of the included patients completed the pruritus questionnaire. The remaining four patients were sent a copy of the questionnaire but none responded. Their data were included in this study without data from the questionnaire. All patients were classified according to the Hurley classification, and 24 out of 34 had a Sartorius score close to (< 6 months) the time of biopsy. 30 out of 34 patients were Hurley II, therefore it was decide to exclude these data from statistical analysis.

Histopathological findings

CD117 identified a higher number of MC in the biopsies than Toluidine Blue, both in lesional skin, ($P < 0.0001$), and in perilesional skin ($P < 0.0001$). The distribution of the MC infiltrate is described in Table 1.

Disease severity and duration

A significant correlation between the MC count in lesional and perilesional skin biopsies was found with CD117 stain ($P = 0.004$); however, this association was not shown with toluidine blue-stained samples ($P = 0.12$).

A significant correlation between MC count and Sartorius score was found [unadjusted $r = 0.25$ (95% CI 0.21–0.38) $P = 0.027$]. This correlation was significant after adjusting for sex and age [adjusted $r = 0$ 0.31 (95% CI 0.01 − 0 0.6) $P = 0.042$]. Disease duration was not correlated with MC count ($P = 0$ 0.25) (Table 2). The ratio of lesional count/perilesional MC count could not be correlated with disease duration.

Pruritus

A statistically significant but clinically insignificant correlation between Sartorius score and itch was found. The perceived itch on the 0–10 scale increased by 0.017 (95% CI 0.016–0.13) points and when adjusted for age and sex, a corresponding increase of 0.084 (95% CI 0.013–0.16) points was found. No correlation between MC count and maximum itch within the past week was found. The reported number

Table 2 Association between mast cells count (CD117) with Sartorius score and disease duration. Univariable and multivariable analysis

	Unadjusted analysis		Adjusted analysis[a]	
	Number of mast cells (95% CI)	*P* value	Number of mast cells (95% CI)	*P* value
Sartorius score	+ 0.25 (0.31–0.48)	0.027	+ 0.31 (0.01–0.60)	0.042
Disease duration	− 0.39 (-0.91–0.12)	0.13	− 0.37 (-1.02–0.28)	0.25

[a]The result was adjusted for age and sex

Table 3 Association between the degree of itching during the past week, number of days of itching during the past month with the number of mast cells and Sartorius score, respectively

	Unadjusted analysis		Adjusted analysis[a]	
	Itching (95% CI)	P value	Itching (95% CI)	P value
Maximum intensity of itch the last week (0–10)				
Number of mast cells (per 1 cell increment)	+0 0.028 (−0.06 to 0.12)	0.53	+0.043 (−0.048 to 0.13)	0.34
Sartorius score (per 1 score increment)	+0.017 (0.016–0.13)	0.014	+0.084 (0.013–0.16)	0.023
Number of days with itch the last month				
Number of mast cells (per 1 cell increment)	−0.12 (−0.46 to 0.22)	0.48	−0.08 (−0.45 to 0.29)	0.65
Sartorius score (per 1 score increment)	0.11(−0.10 to 0.33)	0.29	0.16 (−0.13 to −0.44)	0.26

Univariable and multivariable analysis

[a]The results were adjusted for age and sex

of days with itch, did not appear correlated to neither MC count nor Sartorius Score (Table 3).

Discussion

The presence and number of MC in HS lesions were correlated with disease severity determined by Sartorius score. Sartorius score was also a significant predictor for maximum intensity of itch within the last week. These observations support the hypothesis that MC may be functionally involved in the pathogenesis and development of HS lesions. The increased number of MC and the correlation with disease severity may be helpful for generating hypothesis. However, number of MC could not be correlated with itch or disease duration, possibly due to the more general nature and long-term time scale of these outcome measures. Fluctuations of the number of MC in other tissues have furthermore been described [8]. Moreover, CD117 staining proved to be more sensitive and we only used the MC count obtained by this method for further statistical analysis. Nevertheless, the clinicopathological correlation and the use of a sensitive detection method for MC may be considered strengths of the study, implying the relevance of the hypothesis. The morphological analysis was made on samples of normal-looking perilesional skin of surgical cases, and while the chronicity of the lesions scheduled for surgery may have influenced the morphology of the samples, it is well known that subclinical, early lesions are present in this area supporting the relevance of the study.

The reliance on the retrospective design is an inherent weakness. In addition, 30 out of 34 patients (88.2%) were classified as Hurley II, pointing to a lack of heterogeneity of our population.

In conclusion, HS disease severity measured by the Sartorius score could be correlated to MC count as were the patient reported outcome itch when adjusted for sex and age. The results suggest that MC may be involved in the pathogenesis of HS. It is hypothesized that this takes place through several mechanisms including amongst others keratinocyte activation and IL-17 production.

Compliance with ethical standards

Conflict of interest JCP has been an advisory board member for Abbvie. GBJ has been an investigator, consultant, and advisory board member for Abbvie, InflaRx, InCyte, Leo Pharma, Novartis and UCB; has received unrestricted grants by Abbvie, Leo Pharma and Novartis, and has been a speaker for Galderma; an advisory board member for Janssen-Cilag, Inflarx, MSD and for Pierre-Fabre; and has been an investigator for Regeneron. KZ; EKL and BMN BE, have no conflicts of interest to declare.

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