



Irrelevance of Panton-Valentine leukocidin in hidradenitis suppurativa: results from a pilot, observational study

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Abstract

Panton-Valentine leukocidin (PVL) appears to be a virulence factor which, among others, can exacerbate the pathogenicity of *Staphylococcus aureus* infections, especially inducing severe necrotic, deep-seated skin infections, abscesses, and recurrences. These peculiarities have some overlaps with hidradenitis suppurativa (HS). Our main aim was to assess if *S. aureus* producing PVL could have some role in influencing clinical features and/or course of HS, specifically in the suppuration and recurrence of lesions. This pilot, mono-centric, observational study included all adult subjects affected with HS consecutively referring to our HS clinic over a 3-month period. Clinically evident suppuration and at least 2 weeks wash out from any antibiotic were the main inclusion criteria. Purulent material from HS skin lesions was collected with swabs in order to isolate micro-organisms, with specific regard to *S. aureus*. Detection of PVL was performed by real-time quantitative PCR (RT-qPCR). We also analyzed purulent material from suppurative skin lesions other than HS, as a control. Thirty HS patients were included; 29 purulent lesions (96.7%) harbored at least one bacterial species. Five (16.7%) swab samples were positive for *S. aureus*, none of which was positive for PVL genes. Among the 30 purulent disorders included as controls, 8 (26.3%) were positive for *S. aureus*; of these, 4 strains (50%) expressed LPV. The study results seem to exclude the pathogenetic involvement of *S. aureus* producing PVL in HS; as a result, PVL does not seem to represent a potential target in the future development of HS treatments.

Keywords Hidradenitis suppurativa · Panton-Valentine leukocidin · *Staphylococcus aureus* · Infections · RT-qPCR

Introduction

Hidradenitis suppurativa (HS), also known as acne inversa, is a chronic-relapsing, debilitating inflammatory disease of the hair follicle, which affects apocrine gland-bearing skin, most

commonly the axillae, inguinal regions, anogenital area, and infra- and inter-mammary folds [1]. It is clinically characterized by recurrent, painful, deep-seated nodules commonly ending in abscesses and sinus tracts with persistent suppuration and hypertrophic, bridged scarring. HS usually presents after puberty and its estimated prevalence ranges from less than 0.1 to 4% [1, 2]. HS has a huge negative influence on patients' lives due to its chronic course, pain and other disease-related symptoms, persistent malodor, peculiar anatomical localization, disfiguring sequelae, and lack of a definitive cure [3, 4].

The pathogenesis of HS is not fully recognized and appears to involve a number of interacting factors, including a susceptible genetic background, a dysregulated immune response to various heterogeneous stimuli, and follicular occlusion [1, 2, 5]. The role of bacterial infection in the initiation or propagation of HS remains under investigation [6, 7]. Most frequently bacteriological studies have shown a mixed growth of commensal microbes, which is more consistent with the view that HS is an immune-mediated condition rather than a disease of primary infectious etiology [7, 8]. Bacterial colonization of

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HS lesions may act synergistically with a dysfunctional immune response, involving both the innate and adaptive immune systems, which leads to a chronic, relapsing inflammatory scenario. On the other hand, HS may predispose to an increased risk of skin infections [9]. Panton-Valentine leukocidin (PVL) is a two-component pore-forming cytotoxin produced by *Staphylococcus aureus* inducing leukocyte destruction and tissue necrosis [10]. In addition, PVL is a polymorphonuclear neutrophils priming agent [11]. In keeping with this, it appears to be a highly relevant virulence factor which, among others, can exacerbate the pathogenicity of *S. aureus* infections [12]. In particular, it is related to deep-seated skin and soft tissue infections and causes furuncles, cutaneous abscesses, and severe necrotic skin infections [13, 14]. Moreover, PVL seems to be a marker for severity and recurrence [15]. Based on these assumptions, we were interested in assessing if *S. aureus* producing PVL could have some role in influencing clinical features and/or the course of HS, especially in the suppuration and recurrence of lesions.

Materials and methods

Study design and patients

In the present pilot, mono-centric, observational study, we included all adult subjects affected by HS consecutively referring to our HS clinic over a 3-month period. Patients were excluded in the presence of the following: (i) lack of reliable diagnosis, (ii) absence of clinically evident suppuration, (iii) topical or systemic antibiotics during the 2 weeks before inclusion. Purulent material from HS skin lesions was collected with swabs in order to isolate micro-organisms, with specific regard to *S. aureus* releasing PVL. We also collected purulent material from suppurative skin lesions other than HS, over a 3-month period, as a control. Controls were excluded if they were treated with topical and/or systemic antibiotics or if they had a diagnosis of HS or clinical features resembling HS. The eligible subjects who were visited more than once over the study period underwent skin swabs only at the first visit.

This was a spontaneous survey, with no funding from external sources. The study was approved by the University-Hospital of Ferrara institutional review board. Both patients and controls provided their written informed consent.

Data collection

The following data from HS patients were recorded by using a standardized data collection form: (1) age at inclusion; (2) gender; (3) disease duration, taken as the time between the patient-reported onset of symptoms and/or signs and study inclusion; (4) previous treatments, defined as documented courses with any pharmacological active or surgical

interventions prior to entering this study; (5) current treatment; (6) Hurley stage; (7) sites involved by the disease; (8) number of sites with active suppuration at study inclusion; (9) number of suppurative episodes during the previous 6 months; (10) isolation of microbes, in particular *S. aureus*; (11) Panton-Valentine leukocidin expression by *S. aureus* strains.

From controls, we recorded the following information: (1) diagnosis of purulent skin disorders they were affected by; (2) isolation of *S. aureus*; (3) Panton-Valentine leukocidin expression. These purulent skin disorders were categorized as follows: (i) primary pyodermitis versus secondary pyodermitis/impetiginization of another primary skin disorder; (ii) primarily follicular versus non-follicular purulent disorders; (iii) deep versus superficial inflammatory process.

Microbiological assessments

Samples were collected from the purulent material from HS draining lesions as well as from control suppurative disorders. One sample was collected from a single purulent lesion of each included subject. Content was drained with gentle pressure exercised on previously sterilized skin surface, using sterile gloves and swabs. A suitable transport media for aerobes and anaerobes was used (ESwab Liquid Amies Collection and Preservation System, Catalog No. 490CE.A, Copan Diagnostic, Murrieta, CA, USA). Specimens were stored and delivered to the laboratory according to the manufacturer's instructions.

Swabs from clinical specimens were grown on several selective agar plates to isolate specific organisms, as described above [16]. The *S. aureus* culture suspensions were then stored at 4 °C prior to nucleic acid extraction and PCR analysis. The commercial kit RIDA@GENE PVL assay was used for the extraction of bacterial DNA and for the real-time quantitative PCR (RT-qPCR) analysis through the amplification of a PVL-specific fragment (Panton Valentine Leukocidine lukF-PV). To verify whether cross-contamination had occurred during DNA extraction, purification, and PCR procedures, each sample was processed simultaneously with negative controls, represented by sample lacking DNA (real-time PCR mix). Samples and controls were analyzed in duplicate replica experiments. Samples were run in CFX96 Touch Real-Time PCR Detection System (Applied Biosystems) instrument and sample analysis was performed by Bio-Rad CFX Manager software, following the manufacturer's instructions. Positive and negative controls must show correct results. The positive control had a concentration of 10^3 copies/ μ l. A total of 5×10^3 copies were used in each RT-qPCR run. The RIDA@GENE PVL detection limit was ≤ 5 copies of DNA for the reaction.

Statistics

Continuous variables were presented as mean \pm standard deviation (SD) and categorical variables as frequencies and percentages. Comparisons between groups were made using *t* test for quantitative variables, while Pearson's chi-squared test or the Fisher exact test was used for qualitative variables. For categorical data, odds ratios (OR) with 95% confidence intervals (95% CI) were calculated. All statistical analyses were performed using Stata version 13, setting the significant level α to 0.05.

Results

HS patients

Thirty patients affected by HS were included. Table 1 reports the main HS patients' characteristics. The majority of patients (19 of 30, 63.3%) had a Hurley stage III, 16 (53.3%) had at least 3 different anatomical sites involved by HS, and 9 (30%) reported ≥ 6 episodes of suppuration during the previous 6 months. Seventeen patients (56.7%) had undergone at least 3 previous different treatments and 20 (66.7%) were in treatment with drugs other than antibiotics.

All HS samples but one harbored at least one bacterial species (detailed in Table 2). Five (16.7%) swab samples were positive for *S. aureus*. Isolation of *S. aureus* did not significantly correlate with disease Hurley stage (Hurley stage III had an OR 2.6667, 95% CI: 0.2587 to 27.4865, $p = 0.409$), gender (males had an OR 0.5833, 95% CI: 0.0797 to 4.2711, $p = 0.5957$), previous systemic antibiotics (OR 0.2157, 95% CI: 0.0038 to 12.0965, $p = 0.4553$), patient age ($p = 0.11$), number of involved sites ($p = 0.78$), number of current suppurative lesions ($p = 0.44$), and number of suppurative recurrences during the previous 6 months ($p = 0.15$). Disease duration was higher (18.6 years, SD \pm 11.80) among patients harboring *S. aureus* than among the others (10.1, SD \pm 9.28) ($p = 0.04$). None of the *S. aureus* strains isolated was positive for PVL genes.

Controls

Table 3 shows clinical diagnosis and swab sample data of the 30 purulent disorders included as controls (17 males and 13 females, mean age 39 ± 18.59). Among these samples, 8 (26.3%) were positive for *S. aureus*. Four *S. aureus* strains (50%) expressed PVL. Expression of PVL was strictly related with primary pyodermitis (OR 3.5000, 95% CI: 0.3204 to 38.2337, $p = 0.3044$), primarily follicular inflammations (OR 10.4400, 95% CI: 0.5104 to 213.5310, $p = 0.127$), and deep infectious processes (OR 4.2000, 95% CI: 0.4704 to 37.5001, $p = 0.198$). None of these associations reached the significance threshold, probably due to the small sample sizes.

Discussion

Bacteria have long been considered in the pathogenesis of HS. It is generally acknowledged that bacteria do not play a direct role in the etiology of HS; however, they may be involved in the pathogenesis of HS via follicular dysbiosis and biofilm as well as eliciting an inflammatory response in a genetically predisposing background [7]. Interestingly, it had previously been shown that the microbiological population of HS changes considerably according to the clinical severity of the disease [17]. Our findings support the high prevalence of positive culturing samples from HS lesions [7], since bacteria specimens were isolated from almost all the study samples (29 of 30, 96.7%).

With special reference to *S. aureus*, this has often been described in association with HS and has even been proposed as a potential causative organism [18, 19]. However, the literature includes some controversial data [20] and its action in the pathogenesis of the disease remains unknown. Based on the recognized virulent role of PVL in *S. aureus* infections, especially in those by community-associated methicillin-resistant *S. aureus* (CA-MRSA), also at skin level [21, 22], we wanted to specifically seek its presence in HS lesions. In particular, we were interested in deepening a possible link between *S. aureus* producing PVL and degree of suppuration, skin involvement, disease chronicity, and recurrence. We focused on PVL because it exerts peculiar mechanisms of action that may be in some way compatible with HS. In fact, it induces the release of pro-inflammatory cytokines and nuclear factor kappa B (NF- κ B) in neutrophils, leading to skin infections which tend to be invasive, necrotizing, and recurrent [22, 23]. Analyzing the findings obtained from the purulent skin disorders included as controls, these were fairly consistent with this pathogenic profile (Table 3). Prevalence of PVL-positive *S. aureus* was highly correlated with primary pyodermitis when compared with impetiginized lesions, primarily follicular inflammation and deep inflammatory processes.

The rate of *S. aureus* strains isolated from purulent material drained from abscesses and sinuses of HS patients was quite in line with previous reports, being about 17% [7, 19, 24]. The isolation of *S. aureus* did not correlate with patient or disease characteristics, including severity of HS in terms of Hurley's score, number of sites affected, and frequency of recurrence, unlike what other researchers have found [25]. The most noteworthy finding of our study was that none of the strains of *S. aureus* isolated from HS purulent lesions expressed PVL. This finding strongly suggests an irrelevant role of PVL, not only in HS etiopathogenesis but also in its clinical features and course. Therefore, in speculating about the relevance of *S. aureus* in HS, our results seem to exclude the involvement of PVL. This can also be seen from a therapeutic perspective, since PVL does not seem to represent a potential target in the development of a treatment for HS.

Table 1 Main characteristics of the patients affected with hidradenitis suppurativa

	Total	Males	Females
Patients, <i>n</i> (%)	30 (100%)	21 (70%)	9 (30%)
Age, mean ± SD	33.5 ± 15.05	32 ± 12.7	38 ± 18.23
Disease duration, years, mean ± SD	11.5 ± 10.01	10 ± 9.8	15 ± 9.79
Previous treatments	30 (100%)	21 (100%)	9 (100%)
Systemic antibiotics, <i>n</i> (%)	30 (100%)	21 (100%)	9 (100%)
Topical antibiotics, <i>n</i> (%)	16 (53%)	11 (52%)	5 (56%)
Surgery, <i>n</i> (%)	9 (30%)	7 (33%)	2 (22%)
Biologics, <i>n</i> (%)	7 (23%)	6 (29%)	1 (11%)
Zinc derivatives, <i>n</i> (%)	7 (23%)	5 (24%)	2 (22%)
Systemic retinoids, <i>n</i> (%)	6 (20%)	5 (24%)	1 (11%)
Dapsone, <i>n</i> (%)	6 (20%)	4 (19%)	2 (22%)
Systemic corticosteroids, <i>n</i> (%)	2 (7%)	1 (5%)	1 (11%)
Cyclosporine, <i>n</i> (%)	1 (3%)	1 (5%)	0
One previous treatment, <i>n</i> (%)	5 (16%)	4 (19%)	1 (11%)
Two previous treatments, <i>n</i> (%)	8 (27%)	4 (19%)	4 (44%)
Three or more previous treatments, <i>n</i> (%)	17 (57%)	13 (62%)	4 (44%)
Current treatments	20 (67%)	15 (71%)	5 (56%)
Biologics, <i>n</i> (%)	15 (50%)	11 (52%)	4 (44%)
Zinc derivatives, <i>n</i> (%)	3 (10%)	3 (14%)	0
Systemic retinoids, <i>n</i> (%)	1 (3%)	1 (5%)	0
Cyclosporine, <i>n</i> (%)	1 (3%)	0	1 (11%)
Hurley stage			
I, <i>n</i> (%)	3 (10%)	2 (10%)	1 (11%)
II, <i>n</i> (%)	8 (27%)	7 (33%)	1 (11%)
III, <i>n</i> (%)	19 (63%)	12 (57%)	7 (78%)
Sites involved*, mean SD	2.8 ± 1.3	2.8 ± 1.4	2.8 ± 1
Axillae	25 (83%)	20 (95%)	5 (56%)
Inguinal and anogenital areas	23 (77%)	14 (67%)	9 (100%)
Buttocks	9 (30%)	7 (33%)	2 (22%)
Abdomen	5 (17%)	4 (19%)	1 (11%)
Infra- and inter-mammary folds	3 (10%)	1 (5%)	2 (22%)
Back	2 (7%)	2 (10%)	0
Inner thighs	1 (3%)	1 (5%)	0
One site, <i>n</i> (%)	6 (20%)	5 (24%)	1 (11%)
Two sites, <i>n</i> (%)	8 (27%)	5 (24%)	3 (33%)
Three or more sites, <i>n</i> (%)	16 (53%)	11 (52%)	5 (56%)
Number of sites with active suppuration, mean ± SD	1.5 ± 0.7	1.4 ± 0.73	2.4 ± 1
Number of suppurative episodes during the previous 6 months, mean ± SD	5 ± 5.6	5.7 ± 6.3	5.4 ± 4.3
Isolation of <i>S. aureus</i> , <i>n</i> (%)	5 (17%)	3 (14%)	2 (22%)
Panton-Valentine leukocidin positivity, <i>n</i> (%)	0	0	0

*Patient could have simultaneously more than one anatomical site involved by HS

The role of toxins, especially necrotizing toxins, in HS is uncertain and has been poorly investigated. Diphtheria by the toxigenic zoonotic pathogen *Corynebacterium ulcerans* is increasingly occurring in children, adolescents, and adults. In addition to diphtheria toxin (DT), the exotoxin

phospholipase D (PLD) is considered an important virulence factor of *C. ulcerans* and *C. pseudotuberculosis* [26]. PLD has been found to induce dermonecrotic lesions, increased vascular permeability in vivo, and synergistic hemolysis of sheep blood cells.

Table 2 Bacterial isolates from purulent material drained from hidradenitis suppurativa lesions, other than *S. aureus*

Bacteria	Number (%)
Coagulase-negative staphylococci	16 (53%)
<i>S. epidermidis</i>	7 (23%)
<i>S. haemolyticus</i>	7 (23%)
<i>S. lugdunensis</i>	2 (7%)
Peptostreptococcaceae	8 (27%)
<i>P. anaerobius</i>	5 (17%)
<i>P. asaccharolyticus</i>	1 (3%)
<i>F. magna</i>	2 (7%)
Enterobacteriaceae	9 (30%)
<i>P. mirabilis</i>	6 (20%)
<i>E. coli</i>	2 (7%)
<i>C. diversus</i>	1 (3%)
<i>S. anginosus</i>	2 (7%)
<i>P. bivia</i>	2 (7%)
<i>E. faecalis</i>	1 (3%)
<i>C. striatum</i>	1 (3%)
<i>P. aeruginosa</i>	1 (3%)
<i>A. turicensis</i>	1 (3%)

Pseudomonas aeruginosa can cause severe human opportunistic infections, including many hospital-acquired infections. However, there is scarce evidence about its clinical relevance in patients with HS. Among its toxins, exotoxin A is

Table 3 Purulent skin disorders included as controls

Skin disorder	Number (%)	Isolation of <i>S. aureus</i> , <i>n</i> (% of each disorder)	Panton-Valentine leukocidin expression, <i>n</i> (% of each disorder)
Folliculitis, both superficial and deep	14 (47%)	5 (36%)	3 (21%)
Erysipelas	1 (3%)	0	0
Pustules in acne vulgaris or rosacea	5 (17%)	0	0
Paronychia	2 (6%)	1 (50%)	0
Folliculitis decalvans	2 (6%)	2 (100%)	1 (50%)
Purulent secondary pyodermitis/impetiginizations	6 (20%)	0	0
Subgroups			
Primary pyodermitis	15 (50%)	5 (30%)	3 (20%)
Follicular purulent disorders	16 (53%)	7 (44%)	4 (25%)
Deep inflammation	7 (23%)	3 (43%)	2 (29%)

the main virulence factor [27]. Similarly but less effectively than DT, exotoxin A interrupts protein synthesis in the host cell and has an immunosuppressive action. Pigments, such as pyocyanin, which catalyzes reactive oxygen species (ROS) production and attracts neutrophils, and pioverdin (siderophore), exert multiple detrimental effects on the host too. The blue-green phenazine, pyocyanin, is a key virulence factor that can kill competing organisms as well as host cells and can inactivate catalases to protect against ROS generated by host tissues [28]. Pyocyanin in particular can serve as a redox cyler similar to methyl viologen, resulting in superoxide radical production and oxidative stress [29]. The majority of these virulence factors are under the control of two regulatory systems: the two-component system and the sensing quorum, which allow the survival and multiplication of this microorganism in the host [30].

Despite the inherent potential to cause harmful effects in humans, little is known about the role of these toxins in HS and further investigation could be conducted. Furthermore, the methods used for their detection will still require time for their optimal development and application in this specific context.

This study has some limitations, especially the relatively small number of patients affected with HS included. However, it was designed as pilot in nature and with the possibility of an extension being planned in the event of positive results. The patients attended a tertiary clinic, specifically dedicated to HS, so the study population may be not representative of the entire population affected by this disease and a selection bias cannot be excluded. Other variables, such as comorbidities, body mass index, and lifestyle habits like smoking, potentially relevant for the study assessments, were not considered.

In spite of these limitations, this is the first study to address the potential role of an *S. aureus* virulence factor, like PVL, in HS clinical expression. The results of our study seem to exclude its pathogenetic involvement as well as its relevance in the management of patients.

Author contributions M. Corazza: design of the study, interpretation of data, critical revision of the manuscript. A. Borghi: design of the study, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript. V. Bettoli: design of the study, acquisition of data, critical revision of the manuscript. R. Pora: acquisition of data. I. Bononi, E. Mazzoni, S. Saraceni, and M. Maritati performed the experiments. E. Mazzola: acquisition of data. C. Contini: design of the study, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript. All authors read and approved the final manuscript.

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Data availability All data generated or analyzed during this study are included in this manuscript. Detailed data are available from the corresponding author on request.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethics approval This study received approval from the University-Hospital of Ferrara institutional review board. Approval Number 171174. Approval Date 14/12/2017.

Consent to participate Informed consent was obtained prior to survey participation.

Consent for publication Informed consent was obtained prior to survey participation.

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