



The Relevant Oral Burden of Patients with Hidradenitis Suppurativa

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ABSTRACT

Introduction: Interleukin-17 plays a pivotal role in both hidradenitis suppurativa (HS) and in maintaining oral homeostasis, but their potential link remains unknown. Thus, we aimed to evaluate and quantify the oral burden of patients with HS.

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Methods: In this real-life, multicenter, cross-sectional study, patients with HS were clinically evaluated by two board-certified dermatologists and two board-certified dentists. Oral comorbidities were carefully collected with medical history and therapeutic information.

Results: A total of 102 patients (44.0 ± 0.9 years, body mass index 27.0 ± 2.2 kg/m²) were enrolled. Remarkably, 48% and 43% did not undergo at least an oral hygiene or a dental visit each year, respectively. Oral disorders were found in 55.9% of patients with HS, in particular 39.2% had caries and

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46.7% reported at least one missing tooth. The main oral manifestations in patients with HS were recurrent aphthous stomatitis ($N = 19$, 19.2%), amalgam tattoo ($N = 14$, 14.1%), leukoplakia ($N = 11$, 11.1%), nicotinic stomatitis ($N = 9$, 9.1%), papilloma ($N = 8$, 8.1%), and geographic tongue ($N = 8$, 8.1%). Whilst the main predictor of oral pathological conditions was Hurley staging ($P = 0.0276$), multivariate regression analysis indicated that gender and International Hidradenitis Suppurativa Severity Score System (IHS4) were the main predictors for the presence of caries and number of missing teeth.

Conclusion: As a result of the relevant oral burden in patients with HS, dentists should be part of the multidisciplinary team and oral education should be promoted among patients with HS.

Keywords: Hidradenitis suppurativa; Oral diseases; Teeth; Compliance; Comorbidities

Key Summary Points

Hidradenitis suppurativa (HS) has a relevant oral burden and the main manifestations are recurrent aphthous stomatitis, leukoplakia, and nicotinic stomatitis.

Oral examination should be part of every HS visit.

Dermatologist and dentists should promote oral hygiene in patients with HS.

Dentists may have to join the multidisciplinary HS team.

INTRODUCTION

Hidradenitis suppurativa (HS) is a chronic, multifactorial, inflammatory disorder affecting skin bearing apocrine glands, such as axillary, inguinal, gluteal, and perianal body sites [1]. This recurrent condition is associated with an estimated prevalence of 1–4%, being more frequent in women and with an age onset typically between 20 and 40 years of age [2–6]. Local inflammation spillover of pro-inflammatory cytokines (tumor necrosis factor (TNF α), interleukin (IL)-1 β , IL-12, IL-17, and IL-23) in the circulation sustains the rationale of HS-related comorbidities that may range from autoimmune (e.g., rheumatoid arthritis [7]) to metabolic ones (e.g., non-alcoholic fatty liver [8]) potentially involving the whole body including immunologically privileged areas such as the eye [9].

At the same time, oral manifestations are encountered with high frequency in cases of concurrent autoimmune, autoinflammatory, systemic chronic diseases [10–14]. An overall dysregulation of IL-17 may thus contribute to host alterations that lead to oral microbial dysbiosis. Interestingly, a key role for the IL-17 pathway in the pathogenesis of HS has recently emerged [15], strengthening the possible relationship between HS and oral lesions. Furthermore, HS shares etiopathogenetic similarities with oral lesions, as genetic susceptibility, environmental factors, and immunopathological mechanisms may lead to a dysregulation of the inflammatory response. Common immune-mediated oral diseases include rheumatic disorders, ulcerated, and erythematous lesions, such as recurrent aphthous stomatitis, erythema multiforme and medication-related ulcerations, lichenoid lesions, vesiculobullous lesions, benign migratory glossitis, desquamative gingivitis, and orofacial granulomatosis [16, 17]. Most of these lesions, similarly to HS, characteristically relapse, persist, and frequently recur, and can be the first clinical signs or symptoms of the general disease [18]. All taken together, it is safe to assume that HS may trigger the establishment of several oral manifestations. In view of the above, the aim of the present study

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was to investigate the possible relation between HS and oral lesions in a cohort of patients followed with a multidisciplinary approach involving both dermatologists and dentists.

MATERIALS AND METHODS

Study Design

This is a cross-sectional study enrolling patients with HS (see inclusion and exclusion criteria section) and involving four primary Italian referral centers for both dermatological and oral conditions, namely IRCCS Cà Granda Ospedale Maggiore Policlinico, IRCCS San Raffaele, IRCCS San Gallicano, and Azienda USL Toscana Centro. The study was in line with the Helsinki declaration and approved by the local ethics committee (Study ID 804_2017). All patients signed an informed consent form prior to participating in the study.

Inclusion and Exclusion Criteria

Patients with suspected HS completed the visual-aided questionnaire for the self-assessment of HS, and the final diagnosis was made by two independent board-certified expert dermatologists (> 10 years) and then collected in the hospital dedicated HS database. Then, data were tracked back using keywords such as “teeth”, “tongue”, “oral”, “dental prosthesis”, and “mouth” on the visit text database. Only patients with a proven HS diagnosis and an oral/dental abnormality were enrolled.

Dermatological Evaluation

The dermatological diagnosis of HS was first suggested with the Visual-aided Questionnaire for HS self-assessment [19] and then confirmed with the Dessau criteria [20]. The cutaneous severity was assessed with a static score, the Hurley score [21], and a dynamic one, the International Hidradenitis Suppurativa Severity Score System (IHS4) [22].

Since HS started to be regarded as a systemic inflammatory disease, we decided to adopt also

the Autoinflammatory Disease Damage Index (ADDI) to quantify the overall inflammation due to HS in the enrolled patients [23]. In our centers, before starting systemic treatments, patients with HS underwent a routine oral/dental evaluation.

Dental/Oral Evaluation

Each patient diagnosed with HS underwent meticulous dental examination to evaluate the prevalence of dental caries, the number of missing teeth, and the presence of oral lesions. The complete dentition of patients was considered but excluding third molars. The detection of caries lesions was performed clinically by two board-certified dentists with means of mirror and dental explorer, and radiographically. Prior to assessment, tooth surfaces underwent a dental prophylaxis. Coronal and root caries were examined according to the criteria set by the World Health Organization [24]. The surface was classified as sound when it showed normal enamel translucency after air drying. A decayed tooth was considered as such when presenting a detectably softened, pitted, fissured surface, or showing a shadow under the enamel, or a cavitated lesion, or undermined enamel and dentin. The incipient lesions of white spot were not considered caries. Dental caries was recorded when a lesion felt soft upon probing with the dental explorer. Intraoral bite-wing radiographs were obtained for each subject to confirm the depth of the lesion and to evaluate the presence of dentine occlusal caries and interproximal caries lesions in clinically inaccessible approximal surfaces. Participants were considered to have dental caries if at least one tooth had carious lesions.

A permanent tooth was defined as missing if not present at the clinical examination. Each subject was interviewed to investigate the reason for tooth loss, with the aid of previous radiographs brought by the patient if available. Only teeth lost as a result of advanced carious lesions or periodontal disease were included in the statistical analysis. Teeth extracted because of other reasons not referable to HS, including, but not limited to, agenesis, trauma, oral malignancies, vertical root fractures, endodontic issues and apical periodontitis, tooth

impaction, prosthetic indications, and failure of previous treatments, were not considered.

To detect oral lesions, a careful screening examination was performed through visual inspection and palpation of the oral cavity. Histopathological assessment of tissue samples obtained following biopsies was performed when needed to achieve definitive diagnosis of the lesions.

Finally, patients were asked to quantify on a yearly basis the number of routine dental examinations, and the frequency of professional oral hygiene sessions, self-performed dental hygiene (routine tooth brushing, flossing or equivalent, and the use of toothpastes protecting gum health and against caries).

Statistical Analysis

The Kolmogorov–Smirnov test was applied to analyze the distribution of each variable in order to aid in the choice of parametric or non-parametric tests. Patients were classified on the basis of the presence/absence of oral findings, and the parametric Student *t* test or the non-parametric Mann–Whitney test was performed to identify any difference between the subgroups. Chi-squared test was used to test the association of the frequency between categorical variables while multiple regression analysis (enter approach) was performed to test the impact of independent predictors on the dental outcomes (number of missing teeth, number of dental caries, frequency of dental examination). All parameters were reported as mean \pm standard deviation (SD) or percentages (%). Statistical analysis was carried out with MedCalc Statistical Software version v19.0.3 (MedCalc Software bvba, Ostend, Belgium), and a *p* value lower than 0.05 was considered significant.

RESULTS

Study Population

After the general database of 538 patients with HS was screened, a total of 102 patients (44.0 ± 0.9 years, BMI 27.0 ± 2.2 kg/m²) were

included in this study, with a larger number of women ($n = 59$, 57.8%) than men ($n = 43$, 42.2%). Smokers (51%) were equally distributed between the female ($n = 29$) and male ($n = 23$) population ($P = 0.67$). Most of the patients obtained a high school diploma ($n = 65$, 63.7%) or completed middle school ($n = 26$, 25.5%), while a reduced percentage showed a lower (elementary school: $n = 1$, 1.0%) or higher level of education, such as completing university ($n = 8$, 7.8%) or a PhD ($n = 2$, 2.0%). On the basis of the BMI, patients were categorized as normal weight (BMI < 25 kg/m², $n = 13$, 12.8%), overweight ($25 \leq$ BMI < 30 kg/m², $n = 83$, 81.2%), and obese (BMI ≥ 30 kg/m², $n = 6$, 6%).

Medical Data

In 60.8% of cases ($n = 62$), patients showed a family history of HS. In 39.2% of cases they were the first members of their family to be affected. The average duration of disease was 12.0 ± 6.0 years, ranging from 3 years to 31 years. According to the Hurley score, used to describe three distinct clinical stages of disease, most of the patients were at stage 3 ($n = 78$, 76.5%) followed by stage 2 ($n = 16$, 15.7%) and stage 1 ($n = 8$, 7.8%). The average International Hidradenitis Suppurativa Severity Score System (IHS4) and Autoinflammatory Disease Damage Index (ADDI) were used to evaluate the severity of the disease and to quantify the damage, respectively. The former showed an average value of 8.0 ± 3.4 , ranging from 2.0 to 18.0, while the average value of the ADDI was 2.7 ± 0.9 , ranging from 2 to 5. In our study, adalimumab was the most common treatment ($n = 90$, 88.2%), followed by combination of clindamycin + rifampicin ($n = 6$, 5.9%), clindamycin + rifampicin + metronidazole ($n = 2$, 2.0%), doxycycline ($n = 2$, 2.0%); one patient received infliximab and another secukinumab. All antibiotic therapies were performed for at least 3 months and may have contributed to create oral dysbiosis.

Dental and Oral Data

Out of 102 patients, 43 (42.2%) did not attend any dental examination in 1 year, either for dental prophylaxis or for dental follow-up recalls. Table 1 reports the frequency of attendance at dental examinations. The presence of caries lesions was not reported for 39.2% ($n = 40$) of patients, while the others showed one ($n = 24$, 23.5%), two ($n = 17$, 16.7%), three ($n = 14$, 13.7%), four ($n = 5$, 4.9%), or five ($n = 2$, 2.0%) dental caries. Similarly, 64 patients (62.7%) did not report any missing teeth, while a variable percentage of patients reported a number of missing teeth ranging between 1 and 8. In 55.9% of patients ($n = 57$), several oral findings have been reported in different combinations, as shown in Table 2. A sub-analysis was conducted to investigate any difference between patients showing at least one oral finding and those who did not report any dental manifestation. On the basis of our results, only the Hurley staging was significantly different between the two groups ($P = 0.0276$) (Table 3). Furthermore, the presence of oral findings was not related to a family history of HS ($P = 0.8859$), the gender of patients ($P = 0.05$), the ongoing treatment ($P = 0.5463$), the level of education ($P = 0.4548$), or the smoking habit ($P = 0.2430$).

Interestingly, only 49 (48.0%) performed routine tooth brushing, 13 (12.7%) also flossing and 15 (14.7%) occasionally (> 10 times per month) use protecting toothpastes.

Multivariate Regression Analysis

Multivariate regression analyses were carried out to analyze the impact of independent predictors on the following variables (Table 4):

- Number of missing teeth: our results showed that the variables gender (female), BMI, smoking habit, treatments, IHS4, frequency of dental examination, level of education, and duration of disease can explain 57.21% of the variability observed in our population. However, only the gender ($t = -2.636$, $P = 0.0098$) and the IHS4 ($t = 10.521$, $P < 0.0001$) can significantly contribute to the prediction of the variable “missing teeth”.
- Number of caries: when several variables (gender (female), BMI, smoking habit, treatment, IHS4, frequency of dental examination, the number of emergency examinations, level of education, and duration of disease) were included in our regression model, they were able to explain only 14.88% of the variability observed, while only the gender ($t = -2.127$, $P = 0.0361$) and the IHS4 ($t = 3.977$, $P = 0.0001$) can significantly contribute to the prediction of the variable.
- Attendance at dental examination: the variable included in our multivariate regression analysis (gender, age, BMI, smoking habit, treatment, IHS4, presence of missing teeth, number of caries, level of education, and duration of disease) did not influence the

Table 1 Frequency of dental hygiene and dentistry visits per year in patients with HS

Visits/year	Dental prophylaxis		Dentistry visits	
	Number of patients	% of patients	Number of patients	% of patients
0	49	48.0%	44	43.1%
1	15	14.7%	31	30.4%
2	21	20.6%	16	15.7%
3	8	7.8%	9	8.8%
> 3	9	8.8%	2	2.0%

Table 2 Oral clinical burden of patients with HS

Clinical oral findings	Number of patients	% of patients
Amalgam tattoo	14	14.1%
Epulis ^a	7	7.1%
Erythroplakia	4	4.0%
Herpetic stomatitis	1	1.0%
Leukoplakia	11	11.1%
Lichen planus, erosive type	1	1.0%
Lichen planus, reticular type	5	5.1%
Lichen planus, atrophic type	1	1.0%
Geographic tongue	8	8.1%
Lingua villosa nigra	3	3.0%
Recurrent aphthous stomatitis	19	19.2%
Squamous papilloma	8	8.1%
Pseudocyst	1	1.0%
Ranula	4	4.0%
Squamous cell carcinoma	3	3.0%
Nicotinic stomatitis	9	9.1%

^aAll epulides were biopsied with a diagnosis of fibromatous epulis of the gingiva due to a systemic inflammatory condition (i.e., HS)

attendance at dental examination, explaining only 3.7% of the variability observed.

DISCUSSION

This study explored the potential association between HS and oral lesions. The hypothesis was that the systemic assembly of the inflammasome in HS may trigger the establishment of oral manifestations that share a similar pathogenesis. Such a multiprotein signalling platform is induced by dysregulation of endogenous and exogenous signals and is responsible for the maturation of pro-IL-1 β into mature and bioactive form [2]. Active interleukin-1 β in turn leads to elevation of other cytokine counterparts such as TNF α , IL-1 β , IL-12, IL-17, and IL-23, thus perpetuating the inflammation [3].

Upregulation of IL-17 seems to play a pivotal role in the shift from a symbiotic microbial community to a more complex and aggressive microbiota in the oral cavity [13]. The resultant microbial dysbiosis constitutes a risk predisposing the oral cavity to disease.

The results of the present study support a possible relationship between HS and oral lesions. Indeed, the sub-analysis conducted to investigate any difference between patients showing at least one oral finding and those who did not report any oral manifestations showed a statistically significant correlation with the Hurley staging. It is also worth noting that at least one oral lesion has been observed in more than half of the included patients. The Hurley staging system is one of the most widely used and reliable HS disease severity instruments currently available [25]. This non-quantitative

Table 3 Evaluation of cutaneous, demographic, and oral parameters linked to the presence of oral manifestations in patients with HS

Variable	No oral findings (<i>n</i> = 45)		Oral findings (<i>n</i> = 57)		<i>P</i>
	Mean	SD	Mean	SD	
Age	43.022	8.9201	44.754	9.7143	0.3563
ADDI	2.533	0.7568	2.825	1.0022	0.1708
BMI	27.356	2.1966	26.825	2.2530	0.2080
Number of caries	1.133	1.3751	1.386	1.3196	0.2538
Dental_prophylaxis_year	1.222	1.3633	1.088	1.3267	0.6699
Dentistry_visits_year	0.933	1.0745	0.982	1.0605	0.7922
HS_duration	11.533	5.0972	12.333	6.5991	0.7716
Hurley_score	2.844	0.4240	2.561	0.7075	0.0276
IHS4	8.400	3.2711	7.754	3.5014	0.2656
Missing_teeth	1.000	1.6376	1.263	2.0312	0.6518
Attendance at dental examination	2.156	2.2356	2.070	2.0077	0.9246
Dental emergency visits	1.689	2.1301	1.561	1.8710	0.8925

static tool basically stratifies patients into three stages based mainly on the presence of sinus tracts and scarring. The results observed herein strengthen the hypothesis that oral manifestations might be significantly correlated with the severity of the disease assessed with the Hurley staging system.

In parallel, the results of the present study showed a positive correlation between the IHS4 and the number of missing teeth and caries. The IHS4 has been proposed to overcome the weaknesses of the previous methods in assessing HS severity, such as the absence of an accurate assessment of the extent of inflammation with each disease stage, interpretation difficulties, and time-consuming issues. Therefore, IHS4 has been developed to establish a dynamic HS score based on the quantification of nodules, abscesses, and draining tunnels as the scoring variables [22]. When interpreting the results obtained in the present study, it can be speculated that the severity of HS is strictly correlated with tooth loss and dental caries. Both complications can be triggered by a dysbiosis of the oral microbiota leading to the colonization of

more pathogenic bacteria. The formation of a dysbiotic plaque biofilm nourishes chronic non-resolving and destructive inflammatory responses, which progress through periodontal attachment and bone loss [26]. The mechanism through which these pathogens become dysbiotic is probably via disabling and deregulating the efficacy of the host immune and inflammatory systems, which is already compromised in subjects with HS. This failure to resolve local inflammation induced by bacteria in the periodontium results in a chronic inflammatory state leading to periodontal tissue destruction [27]. In this respect, emerging evidence suggest that IL-17 dominates the inflammatory network characteristic of periodontitis, further supporting the association between HS and periodontal disease [28]. The extensive loss of the tooth attachment apparatus in severe periodontitis ultimately results in tooth loss, which can explain why a severe HS stage can be associated with the higher number of missing teeth observed in the present study. Apart from periodontitis, dental caries has also been recognized as a main cause of tooth loss. Interestingly, the

Table 4 Multiple regression analyses evaluating missing teeth, caries, and dental examination

Independent variables	Coefficient	Standard error (SE)	<i>t</i>	<i>P</i> value	<i>r</i> _{partial}	<i>r</i> _{semipartial}
Number of missing teeth						
(Constant)	1.7340					
Gender	− 0.7071	0.2682	− 2.636	0.0098	− 0.2650	0.1716
Age	− 0.004327	0.01734	− 0.250	0.8035	− 0.02601	0.01624
BMI	− 0.1152	0.05951	− 1.935	0.0560	− 0.1978	0.1260
Smoking habit	0.1527	0.2493	0.613	0.5417	0.06373	0.03987
Treatment	0.07795	0.1529	0.510	0.6115	0.05307	0.03318
IHS4	0.3930	0.03735	10.521	< 0.0001	0.7390	0.6848
Attendance at dental examination	− 0.04342	0.06060	− 0.716	0.4755	− 0.07449	0.04664
Level of education	− 0.1038	0.1906	− 0.545	0.5872	− 0.05671	0.03546
HS duration	0.02165	0.02561	0.846	0.4000	0.08782	0.05504
Number of caries						
(Constant)	2.4740					
Gender	− 0.5414	0.2546	− 2.127	0.0361	− 0.2165	0.1952
BMI	− 0.07249	0.05736	− 1.264	0.2095	− 0.1306	0.1160
Smoking habit	− 0.04059	0.2508	− 0.162	0.8718	− 0.01687	0.01485
Treatment	− 0.08102	0.1553	− 0.522	0.6031	− 0.05431	0.04789
IHS4	0.1593	0.04005	3.977	0.0001	0.3830	0.3651
Attendance at dental examination	0.1048	0.06239	1.680	0.0964	0.1725	0.1542
Emergency checkup	− 0.03726	0.06991	− 0.533	0.5953	− 0.05548	0.04893
Level of education	− 0.1830	0.1937	− 0.945	0.3472	− 0.09804	0.08674
HS Duration	0.01627	0.02153	0.755	0.4519	0.07852	0.06935
Attendance at dental examination						
(Constant)	0.4396					
Gender	0.1801	0.4706	0.383	0.7029	0.04008	0.03736
Age	0.006709	0.03052	0.220	0.8265	0.02304	0.02146
BMI	0.07294	0.1041	0.701	0.4852	0.07327	0.06843
Smoking habit	− 0.3137	0.4212	− 0.745	0.4583	− 0.07784	0.07273
Treatment	0.3305	0.2575	1.283	0.2027	0.1333	0.1253
IHS4	− 0.1162	0.09414	− 1.234	0.2202	− 0.1283	0.1205
Missing teeth	− 0.1847	0.1783	− 1.036	0.3030	− 0.1079	0.1011
Number of caries	0.3448	0.1797	1.918	0.0582	0.1972	0.1873
Level of education	0.01432	0.3239	0.0442	0.9648	0.004636	0.004318

Table 4 continued

Independent variables	Coefficient	Standard error (SE)	<i>t</i>	<i>P</i> value	<i>r</i> _{partial}	<i>r</i> _{semipartial}
HS duration	0.003345	0.04445		0.0753	0.9402	0.007889

progression of dental caries and periodontal diseases involves positive feedback loops. In caries, the exposure to dietary sugars and fermentation to organic acids can result in a positive feedback loop resulting in increased proportions of acidogenic and aciduric species which enhances the acidity of the environment. In gingivitis, plaque accumulation at the gingival margin leads to inflammation and a positive feedback loop resulting in ever-increasing proportions of inflammophiles [29]. This supports the strong association between dental caries and tooth loss found in the present study.

It is also worth mentioning that IL-17 secreted by the subset T helper 17 triggered by a dysbiotic microbiome is a crucial modulator to mediate oral mucosal immunopathology [14]. IL-23 also appear to have a pathogenic profile able to induce inflammatory or autoimmune disease, promoting T helper 17 cell expansion during inflammatory bone loss [30]. In this context, IL-17 and IL-23 functions are critical for protective immunity but also for the pathogenesis of diseases at barrier sites. As such, the dysregulation of IL-17 and IL-23 observed in patients with HS may explain the inflammation and attachment loss in the oral cavity, leading to the significant number of oral manifestations, missing teeth, and dental caries detected in the present study.

CONCLUSION

As a result of the nature of the study (cross-sectional) we only highlighted the oral burden in patients with HS, suggesting that dentists should also be part of the HS multidisciplinary team. Dental prophylaxis and dentistry visits are of paramount importance to maintain quality of life and proper digestion, two parameters particularly important in patients with chronic diseases. Dental-dermatological

cooperation should be improved to create intra-hospital ad hoc integrated care pathways for patients with HS, especially those who are candidates for biologics that have to undergo a mandatory oral health evaluation. Dental prophylaxis should be promoted each 3 months in patients with HS and further studies are needed to understand the impact of HS therapies on oral comorbidities (i.e. epigenetics [31–33] and resistome).

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Ethical Approval. The study was in line with the Helsinki declaration and approved by the local ethics committee (Study ID 804_2017). All patients signed an informed consent form prior to participating in the study.

Data Availability Statement. The datasets generated during and/or analyzed during the current study are available from the corresponding author (G.D.) on reasonable request.

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