Anemia in hidradenitis suppurativa: a retrospective cohort study

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1. Abstract in English

Background:
Hidradenitis suppurativa (HS) is a chronic inflammatory disease characterized by abscesses, sinus tracts and scarring in apocrine gland bearing regions. There is no clear consensus regarding the co-occurrence of HS and anemia. The purpose of our study is to determine the prevalence of anemia and risk factors for anemia in our HS cohort.

Methods:
We conducted a retrospective case series of 104 HS adult patients seen at the Montreal General Hospital from 2015-2019. The variables recorded included: age, sex, ethnicity, smoking status, diabetes, hypertension, inflammatory conditions, Hurley staging, hemoglobin, mean corpuscular volume and hematocrit. Females with a Hb < 120mg/dL, and males with a Hb < 130mg/dL were considered as having anemia. The association between anemia and the variables collected were assessed via univariate logistic regression. Significant associations ($p < 0.05$) were included in a multivariate logistic regression model.

Results:

Thirty (28.9%) patients in our cohort were anemic. On univariate analysis, diabetes OR 4.12 95%CI [1.28,13.18], and patients of African-Canadian origin OR 4.03 95%CI [1.11,14.49] were found to be associated with increased odds of having anemia. When diabetes and ethnicity were controlled for on multivariate analysis, patients with Hurley II and Hurley III had increased odds of developing anemia compared to Hurley I (OR 7.56 95%CI [1.39,40.89], and OR 12.62 95%CI [2.24,71.15], respectively)

Conclusion:
Anemia was found to be highly prevalent in our HS cohort (28.9%), and HS disease severity, diabetes and being of African origin were found to be associated with increased odds of having anemia.

2.Abstract in French

Introduction:
L'hidrosadénite suppurée (HS) est une maladie inflammatoire chronique caractérisée par des abcès, des trajets fistulaeux et des cicatrices dans les régions portant des glandes apocrines. Il n'y a pas de consensus clair concernant la co-occurrence de l'HS et de l'anémie. Le but de notre étude est de déterminer la prévalence de l'anémie et les facteurs de risque d'anémie dans notre cohorte HS.

Méthodes :
Nous avons mené une série de cas rétrospectifs de 104 patients adultes atteints d'HS vus à l'Hôpital général de Montréal de 2015 à 2019. Les variables enregistrées comprenaient : l'âge, le sexe, l'origine ethnique, le statut tabagique, le diabète, l'hypertension, les conditions inflammatoires, le stade de Hurley, l'hémoglobine, le volume corpusculaire moyen et l'hématocrite. Les femmes avec une Hb < 120 mg/dL et les hommes avec une Hb < 130 mg/dL ont été considérés comme anémiques. L'association entre l'anémie et les variables recueillies a été évaluée par régression logistique univariée. Des associations significatives ($p < 0,05$) ont été incluses dans un modèle de régression logistique multivariée.

Résultats:

Trente (28,9 %) patients de notre cohorte étaient anémiques. En analyse univariée, le diabète OR 4,12 IC à 95 % [1,28, 13,18] et les patients d'origine noire OR 4,03 IC à 95 % [1,11, 14,49] se sont avérés associés à une probabilité accrue d'avoir une anémie. Lorsque le diabète et l'origine ethnique étaient contrôlés en analyse multivariée, les patients atteints de Hurley II et de Hurley III présentaient un risque accru de développer une anémie par rapport à Hurley I (OR 7,56 IC à 95 % [1,39 ; 40,89] et OR 12,62 IC à 95 % [2,24 ; 71,15], respectivement)

Conclusion:
L'anémie s'est avérée très répandue dans notre cohorte HS (28,9 %), et la gravité de la maladie HS, le diabète et le fait d'être d'origine africaine se sont révélés être associés à une probabilité accrue d'avoir une anémie.

3. Acknowledgements

I would like to thank Dr. Ivan Litvinov, Dr. Elizabeth O'Brien, Dr. Mathieu Powell, Dr Suhad Ali and Dr. Denis Sasseville for their support for my master's thesis.

4. Contribution of the authors

Anjali Saxena conducted the chart review, data collection, statistical analysis and write up of the thesis and manuscript

The remaining authors provided advice, funding, supervision and support during the research process, manuscript preparation and while reviewing the manuscript.

5. List of tables:

6. Abbreviations

Anterior pharynx defective 1 (APH1)
Benzoyl peroxide (BPO)
Body mass index (BMI)
C-reactive protein (CRP)
Cutaneous T cell lymphomas(CTCL)
Dermatological life quality index (DLQI)
Food and drug administration (FDA)
Hidradenitis suppurativa physician global assessment (HS-PGA)
Inflammatory bowel disease (IBD)
Intense pulse light(IPL)
Interleukin (IL)
International review board (IRB)
Keratin 17 (KRT17)
Keratin 6A (KRT6A)
Matrix metalloproteinases (MMPs)
Mean corpuscular volume (MCV)
Methicillin resistant S.aureus (MRSA)
microRNA (miRNA)
Neodymium-doped yttrium aluminum garnet (Nd:Yag)
Presenilin enhancer 2 (PSENEN)
Pyoderma gangrenosum, acne and hidradenitis suppurativa (PASH)
Pyogenic arthritis, pyoderma gangrenosum, acne and hidradenitis suppurativa (PAPASH)
Quality of life (QOL)
Regulated and activation normal T cell expressed and secreted (RANTES)
Squamous cell carcinomas (SCCs)
Staphylococcous aureus (*S.aureus*)
Tumour necrosis factors alpha (TNF-α)

7. Introduction

The objective of this study is to determine the prevalence and risk factors for the development of anemia in patients with hidradenitis suppurativa.

8. Comprehensive review of the relevant literature

Hidradenitis suppurativa (HS) is a chronic inflammatory skin condition that affects apocrine gland bearing areas, most often the axillary, intra and infra-mammary, inguinal and anogenital regions [1] . HS is characterised by recurrent follicular inflammation and scarring. Clinically, patients with HS present with painful inflammatory nodules, abscesses, sinus tracts and fistulas all of which can be pruritic, painful and malodorous. If persistent, patients can develop contractures and malignancies such as squamous cell carcinomas[2]. HS is often misdiagnosed for other dermatological conditions including folliculitis, cysts, and acne, prolonging the time to diagnosis. Additionally, treatment options for HS have limited efficacy and consequently patients often suffer physically while also having higher rates of anxiety, depression and lower work productivity[3].

i. Epidemiology

The true prevalence of HS remains unclear. Prevalence estimates range from 0.00033% to 4.1% [4]. This wide range could be attributed to variations within the geographic locations where the populations were studied and the burden of misdiagnosed or undiagnosed disease [4]. Additionally, the 4.1% was from a Danish population with sexually transmitted diseases, and hence is likely an outlier[5]. The largest retrospective US study conducted in 2017 sampled over 40 million patients and determined the prevalence of HS to be 0.1% [6]. Few other US population

based studies evaluating the prevalence of HS have been conducted and include a 2007 study which sampled 15 million US patients and determined the prevalence of HS to be closer to 0.053%[7]. Women are two to three times more likely to be affected by HS as compared to men [6, 8-13] and in the United States, African-Americans and biracial patients (white and African American) are more likely to develop HS as compared to Caucasian patients[6, 14-17]. The prevalence of HS is highest amongst patients in the third and fourth decade [6]. Overall, HS is an uncommon but not rare disease.

ii. Pathogenesis

The pathogenesis of HS has not fully been elucidated, however, the process appears to be heralded by follicular hyperkeratinisation which leads to follicular obstruction and dilation. The follicle eventually ruptures, and the release of its' contents causes inflammation which leads to long term structural changes to the follicle and surrounding tissue. Endogenous factors in genetically predisposed individuals and exogenous factors such as smoking, obesity, metabolic syndrome contribute to the pathogenesis of HS.

The initiator of follicular hyper-keratinization has not been clearly identified, however, microRNAs (miRNAs) are suspected to play a role. miRNAs are regulators of inflammation and modulate the innate and adaptive immune response[18]. It has been postulated that dysregulation of follicular miRNA primes the lesional keratinocytes to produce pro-inflammatory cytokines (interleukin 1B (IL-1B) and regulated and activation normal T cell expressed and secreted (RANTES) along with secretion of anti-microbial peptides (e.g., psoriasin and calgranulin) [18,

19]. These events promote follicular hyper-keratinization which leads to follicular obstruction/occlusion and subsequent dilation. The follicle eventually ruptures, releasing its' contents into the dermis and epidermis leading to an acute and severe inflammatory response[1, 20]. Chronic and recurring inflammation leads to scarring and fibrosis with the development of sinus tracts and fissures. Genetic factors, upregulation of inflammatory cytokines, hormones, environmental and physical factors all play a role in the development and persistence of HS lesions.

a) Genetic factors

Thirty to 40% of patients with HS patients have ≥1 family member affected by the disease [1]. Mutations in a range of genes including *PSENEN*, *PSEN1* and *NCSTN* involved in the γ-secretase and NOTCH signalling pathway, and defects in the inflammasome related *PSTPIPI1* genes have been found to be associated with HS.

γ-secretase and NOTCH signalling pathway

NOTCH receptors are transmembrane proteins which are cleaved by γ-secretase. Once cleaved, activated NOTCH enters the cell nucleus and activates genes involved in epidermal and follicular differentiation and proliferation [21]. The γ-secretase complex is composed of 4 subunits: presenilin, presenilin enhancer 2 (PSENEN), nicastrin and anterior pharynx defective 1 (APH1)[1]. The respective genes encoding these proteins are *PSEN1/2, PSENEN, NCSTN* and *APH1A/B* [21]. In 2010, Wang et al. conducted a genome wide linkage scan and subsequent haplotype analysis in 6 Han Chinese families that demonstrated autosomal dominant inheritance of HS. In family 1, a frameshift mutation in *PSENEN* gene was identified[22]. This mutation was

not present in the unaffected family members and the general Han Chinese population. A different *PSENEN* mutation was found in family 2. In families 3-6, gene mutations in *NCSTN* and *PSEN1* were identified[22]. Deficiency of γ – secretase in mouse models resulted in conversion of hair follicles to epidermal cysts and absorption of sebaceous glands [23]. In a human clinical trial, γ-secretase inhibitor nirogacestat was administered to 17 adults of which six patients developed follicular and cystic lesions in intertriginous regions [24], recapitulating the clinical features of HS in affected patients. Additionally, mice deficient in *Notch 1, 2 or 3* exhibit a phenotype similar to γ – secretase deficient mice, keeping with the role of γ – secretase in NOTCH signal transduction[23, 25].

Inflammasome dysfunction

Hidradenitis suppurativa patients have marked upregulation of IL-1β in their lesional skin[26]. IL-1β is produced by an intra-cellular protein complex called the inflammasome[27]. The inflammasome is composed of a damage sensing protein of the NOD like receptor, example NLPR3, which downstream activates caspase 1[28]. Caspase 1 subsequently activates pro IL-1β into its active form IL-1β . IL-1β production leads to the production of chemokines which leads to a massive influx of inflammatory cells including neutrophils and it is this neutrophilic inflammation that contributes to the purulent nature of HS lesions[26]. Furthermore, IL-1β enhances secretion of matrix metalloproteinases (MMPs), which results in tissue destruction, another characteristic clinical feature of HS[26]. Aberrant activation of the inflammasome leads to auto-inflammatory conditions and interestingly, patients with HS often have associated auto-inflammatory conditions such as pyogenic arthritis, pyoderma gangrenosum, acne and hidradenitis

suppurativa (PAPASH) and pyoderma gangrenosum, acne and hidradenitis suppurativa (PASH)[28].

PAPASH has been found to be due to a mutation in the gene *PSTPIP1*. *PSTPIP1* along with pyrin (encoded by the *MVEF* gene) plays a role in inflammasome assembly[28]. Mutations in *PSTPIP1* lead to increased IL-1β activation resulting in a neutrophil mediated auto-inflammatory response[28]. PSTPIP1 is also cleaved by the γ-secretase complex, providing a potential link between γ-Secretase function and the inflammasome[29]. Mutations in the NOD signalling pathway, *MEVF, NLRP3* and *PSTPIP1* have been identified in patients with PASH, elucidating the role of defects in the inflammasome in patients with HS[28].

Other genes implicated in HS

Other genes found to be associated with HS include *Keratin 17 (KRT17)* and *keratin 6A (KRT6A), FGFR2* and the β-defensin gene cluster.

b) Important Immune mediators of HS

Interleukin-17 (IL-17)

IL-17 levels are elevated in lesional and peri-lesional skin of HS patients as compared to healthy controls[30]. CD4+ T cells, once stimulated by IL-23, are transformed into TH17 cells that secrete IL-17[1]. IL-17 subsequently induces the production of IL-1β and TNF-α. IL-1β activation results in auto-inflammatory neutrophilic response (see above) and also leads to further activation of TH17 cells[30]. TNF-α is a pro-inflammatory cytokine, which also activates the TH17

inflammatory pathway and leads to inflammation in HS lesions through different mechanisms (see below). This self-sustaining feedback loop of inflammation attributes to the chronicity and recurrence of HS.

Randomized clinical trial was published in Lancet and should be cited in the thesis. Please check that other pivotal trials are cited in the thesis:

Tumor Necrosis Factor alpha (TNF-α)

TNF-α is a pro-inflammatory cytokine produced by macrophages and monocytes and expressed in the basal layer of the epidermis, sweat glands and hair follicles[31]. Patients with HS have been found to have higher levels of TNF-α levels in their serum and lesional peri-lesional tissue [31]. Additionally, TNF-α levels increase with increasing HS disease severity and can be used to monitor disease activity.

TNF-α induces its inflammatory effects by activating the TH17 pathway which leads to increased inflammation via the IL-1β inflammasome pathway[32]. TNF-α also activates MMP2 and MMP9 which causes inflammation and tissue injury[32]. Secondary effects of TNF-α include decreased production of adiponectin which is produced by adipocytes. Adiponectin plays a role in regulating glucose metabolism and insulin sensitivity. Patients with HS have a significantly higher risk of developing diabetes and metabolic syndrome as compared to healthy controls[33] and patients with HS have been found to have lower levels of adiponectin irrespective of age, sex and body mass index (BMI)[34].

Other cytokines

Other cytokines that are potentially implicated in HS include IL-23 which activates Th17 cells, IL-12/23 and IFN-γ. Further studies are required to determine the role of these cytokines in HS.

c) Hormonal associations with HS

Given that HS is more common in women, and in some patients, disease intensity fluctuates with menstrual cycles, hormones have been suggested to play a role in the pathogenesis of HS[35]. Patients on spironolactone, an androgen antagonist have lower Hidradenitis suppurativa physician global assessment (HS-GPA) scores and lesion counts as compared to controls[36], implicating androgens as a target for HS treatment. However, patients with HS do not appear to have a higher level of serum sex hormones, and if androgens do play a role in HS, it is likely at the level of the follicle itself[36].

d) Smoking and HS

Studies have shown that the prevalence of HS in smokers is nearly double that than non smokers. The odds of a new HS diagnosis increased by 90% in tobacco smokers, in one study[37]. HS patients who smoke have been reported to have more severe disease and more body regions involved[38]. The relationship between smoking and HS has not clearly been eludcidated, however, it has been reported that cigarette smoking induces the expression of TNF-alpha in human keratinocytes[39] and downregulates the NOTCH pathway[40].

iii. Clinical presentation

Typically hidradenitis suppurativa lesions are found in intertriginous areas such as the inguinal, inframammary and axillary regions, however, the disease can affect any region with skin-to-skin contact including the posterior neck, medial thighs and pannus[41]. HS typically has an insidious onset with discomfort, pain and pruritus at affected site followed by the formation of a painful, deep-seated nodule that drains purulent, malodourous fluid[42]. These nodules can remain dormant for days to years. With disease progression, nodules recur and adjacent nodules subsequently coalesce together forming an abscess[41]. Multiple abscesses progressively connect with each other, leading to the formation of sinus tracts. Sinus tracts are persistent and painful and rarely resolve in the absence of surgical intervention[41]. Given the non-specific clinical features, HS lesions can be misdiagnosed as numerous different conditions including carbuncles, furuncles, infection such as cellulitis and epidermoid cysts[6]. Double headed comedones are a clinical finding that is more specific to HS and can help differentiate from other causes[6]. The chronic inflammatory nature of this condition can lead to scarring and stricture formation, resulting in decreased mobility[41]. Additionally, chronic HS wounds can be pre-disposed to higher rates of squamous cell carcinomas (SCCs).

iv. Physician reported assessment score

Given the non-specific cutaneous manifestations of HS and high variability of individual clinical presentations, no single outcome measure has be identified in classifying HS disease severity and as a consequence, up to 20 different staging instruments have been proposed thus far[43]. One of the most widely used staging scales, the Hurley staging scales was first established in 1989[44].

The Hurley score, classifies patients into 3 stages, allowing for appropriate treatment modality based on the stage. Stage 1 is characterised by single or multiple abscesses in the absence of sinus tracts and scarring and warrants medical treatment only. Stage 2 has more abscesses that are widely separated and sinus tracts and scarring, requiring both medical and local surgical treatments. Stage III is characterised by numerous abscesses with diffuse or nearly diffuse involvement of the affected area, and extensive sinus tracts and scarring. The latter patients require medical treatments along with extensive wide surgical treatments[44]. The Hurley score allows for the assessment of damage caused by the disease but is not optimal for the evaluation of disease evolution and treatment response.

The Hidradenitis Physician Suppurativa Global Assessment score (HS-PGA) categorizes patients into 6 different levels, based on four clinical findings, the number of abscesses, the number of draining fistulas, the number of inflammatory nodules and presence or absence of non-inflammatory nodules[45].

The HiSCR severity scale is based on the same items as the HS-PGA and provides a score based on the improvement between two time points. Responders are qualified as patients who had “at least a 50% reduction from baseline in the abscesses and inflammatory nodules count, with no increase of abscesses or draining fistulae count” vs. non responders who did not meet the above criteria. The HiSCR has been used widely for clinical studies[45].

The IHS4 score was established in 2017 and uses the same parameters as the HS-PGA and HiSCR score and compiled them into a formula:

IHS4= nodules + 2 (abscesses) + 4 (draining fistulas)

A score of 0-3 qualifies as mild disease, moderate 4-10 and severe >11[45].

v. Management of hidradenitis suppurativa

Topical agents

Studies regarding topical agents for HS are limited. Antiseptics such as benzoyl peroxide (BPO) and chlorhexidine are often prescribed, however, evidence for these agents is limited. Rescorcinol (15%), has proven to be effective in some studies[46].

Intralesional therapies

Intralesional triamcinolone acetonide (10mg/ml) injections are often injected into active HS nodules and has been referenced in best practise guidelines. A prospective case series evaluated the effect of intralesional corticosteroids on HS lesions and noted significant reductions in physician assessed erythema, edema, suppuration and size[47]. Intralesional corticosteroid injections can be used as monotherapy or as an adjuvant to systemic medical or surgical therapies.

Antibiotics

Hidradenitis suppurativa lesions can become secondarily infected and hence both topical and systemic antibiotics have been used in the management of this condition. Topical clindamycin (0.1%) twice daily is considered to the be the first line treatment for mild to moderate HS as it has coverage against both staphylococcal and streptococcal species[48]. Oral antibiotics that are

commonly prescribed for HS include a combination of clindamycin and rifampin for up to 10 weeks, ampicillin, fluoroquinolones and tetracyclines to name a few. More recently, a pilot study in a cohort of 30 consecutive patients reported that HS patients treated with a 6 week course of ertapenem had a significant decrease in median sartorius score[49]. Morevoer, at 6 months of treatments, 59% of HS affected regions had achieved remission[49]. Certain antibiotics, such as tetracyclines have the added benefit of also having anti-inflammatory properties which also helps in the treatment of HS. Given the increasing rate of resistance, namely clindamycin resistant staphylococcous aureus (*S.aureus*) and ciprofloxacillin resistant methicillin resistant S.aureus (MRSA) , the use of long-term antibiotics is limited in the management of HS[50].

Anti inflammatory treatments

The inflammation associated with HS has been targeted using various anti-inflammatory treatments. These include but are not limited to anti-neutrophilic medications such as dapsone and colchicine and retinoids such as acitretin. Prednisone and cyclosporine are used for immediate relief of symptoms, however, are not long-term treatment options. More recently, new monoclonal antibodies have gained regulatory approval in the treatment of HS and continued to be studied on a regular basis.

Dapsone

No randomized control study for the role of dapsone in the treatment of HS exists. Based on a systematic review of seven studies, with a cumulative patient population of 135 patients, 62.2% of patients had varying degrees of improvement in their HS score[51]. However, out of the seven

studies, only three used dapsone as monotherapy, confounding the results[51]. The evidence for the use of dapsone for the treatment of HS is overall weak.

Colchicine

Colchicine works on the IL-1B pathway, which may play a role in HS pathogenesis and hence has been used in the management of HS. In a prospective series of 20 patients, colchicine when used as monotherapy or when used in combination with minocycline, resulted in a significant improvement in PGA and dermatological life quality index (DLQI) patient scores[52]. The evidence, although not robust, supports the use of colchicine in HS patients.

Acitretin

Oral retinoids are commonly used in conditions that affect the hair follicles, the most common use being for acne vulgaris. Given that HS is condition that is defined by a disorder of the follicular unit, acitretin is used for the treatment of moderate to severe HS. A retrospective cohort study published in 2023, included sixty-two patients with moderate to severe HS who had failed to respond to topical therapies. A significant decrease in IHS4 scores was found at 12 weeks in responders and the reported side effects were limited. The use of acitretin has been incorporated into treatment guidelines for HS[53].

Anti-diabetics- Metformin

Metformin is an anti-diabetic medication that mediates its effects through lowering insulin resistance and insulin levels. Metformin has also been found to decrease TNF levels, a cytokine

which is elevated in patients with hidradenitis suppurativa[54]. A systematic review in 2023, identified 117 HS patients in the literature who had received metformin as monotherapy. The outcomes measures varied widely between the studies, however, majority of patients report improvement in disease severity and quality of life. One study of 11 patients demonstrated no symptoms improvement[54]. The small studies with limitation in the methods, warrant the need for further studies to determine the role of metformin in the treatment of HS.

Biologics

Adalimumab

Adalimumab is a recombinant human IgG1 anti-tumor necrosis factor alpha antibody that is the only biologic treatment approved for HS. The PIONEER I and II study in total had 633 patients with HS and reported a significantly higher clinical response rate at 12 weeks in patients who had received adalimumab 40mg weekly compared to placebo (41.8% vs 26.0% ($p=0.003$) in PIONEER I and 58.9% vs 27.6% ($p<0.001$) in PIONEER II)[55]. Side effect profile was similar in both groups. This study spearheaded the food and drug administration (FDA) approval of adalimumab for patients with moderate to severe hidradenitis suppurativa.

Ustekinumab

Ustekinumab is a IgG1 monoclonal antibody that binds to the p40 subunit of IL 12 and IL 23. In a literature review conducted by *Martora et al*. out of 49 patient with moderate to severe HS, 38 patients (78%), reported a reduction in IHS4, HS-PGA and HiSCR scores[56]. The quality of evidence supporting the use of ustekinumab is poor and is based on case series and retrospective studies.

Secukinumab

Secukinumab is an anti IL-17 medication. In the SUNSHINE trial, administration of secukinumab every 2 week demonstrated a significant decrease in HS severity as compared to placebo. These patients responses were sustained until the end of trial at 52 weeks. The most common side effect reported was headache and the medication had a relatively favorable safety profile[57].

Anakinra

Anakinra is a monoclonal a recombinant IL-1 receptor antagonist. In a double-blind, randomized, placebo-controlled trial of 20 patients, 20% of placebo patients reported a decrease in disease activity scores versus 78% of patients who had received anakinra ($p=0.02$)[58]. Additionally, new HS exacerbations presented at a later duration in patients who had received anakinra compared to the placebo group[58].

Surgical and laser treatments

Surgical treatments for hidradenitis suppurativa range from incision and draining of fluctuant nodules to local excisions and wide local excisions. Surgical intervention is required for the definitive treatment of sinus tracts and scar tissues. Lasers that can be used in the treatment of HS include neodymium-doped yttrium aluminum garnet (Nd:Yag) , alexandrite and light based treatments such as intense pulse light(IPL) [59].

9. Manuscript: Determining the prevalence and risk factors for anemia in patients with hidradenitis suppurativa- a retrospective cohort study

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Introduction

Hidradenitis suppurativa (HS) is a chronic inflammatory disease characterized by abscesses, sinus tracts and scarring in apocrine gland bearing regions[7]. Although the exact pathogenesis is not known it has been suggested that HS is heralded by follicular rupture which leads to extrusion of bacteria, sebum and hair into the dermis and initiates a chronic inflammatory response[55]. An inflow of neutrophils, lymphocyte and histiocytes leads to abscess formation and bacterial superinfection. Chronic recurrences lead to sinus tract formation and scarring[55].

Anemia is defined as Hgb <130mg/dL in men and <120mg/dL in women. Iron deficiency anemia is the most common type of anemia, followed by anemia of chronic disease[60]. Anemias can commonly be seen in patients with inflammatory conditions, malignancies and auto-immune diseases. In states of chronic inflammation, increased hepcidin production results in increase uptake of iron into the inflammatory cells. This results in decreased available iron for hematopoietic function leading to anemia[61]. Additionally, in inflammatory conditions, elevated

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TNF alpha levels also lead to increased degradation of red blood cells and decreased erythropoiesis[61].

Hidradenitis suppurativa has been known to be associated with physical and psychological comorbidities. Despite the inflammatory nature of this condition, the association between anemia and HS has not been widely understood. A 1968 study of 48 HS patients showed that 24% had marked anemia at levels <100mg/dL[62]. A cross sectional Danish study in 2015 with 462 HS patients concluded that patients with HS did not have an increased prevalence of anemia as compared to control group and there was no correlation between disease severity and anemia[63]. In 2019, Soliman et al conducted a retrospective analysis of 1,413 patients and reported that HS patients were 2.20 times more likely to develop anemia as compared to acne vulgaris patients[64]. A 2020 publication concluded that the prevalence of anemia was higher in the HS population as compared to the general population and sex, African American ethnicity and non smoking status were risk factors for anemia in HS patients[65]. Smoking has significant impact as it causes increased blood leukocytes, neutrophils, lymphocytes, and monocytes, as well as increased hematocrit, hemoglobin, and mean corpuscular volume[66].The lack of consensus regarding anemia and HS and the heterogeneous findings prompt further studies to better determine the relationship of these two variables and to add to the literature on this topic.

Purpose of study:

1) To determine the prevalence of anemia in our HS population
2) To determine whether there is a correlation between HS disease severity, as determined by the Hurley stage, and risk of developing anemia
3) Determining risk factors for anemia in patients with HS

Hypothesis:

Given the role of inflammation in the pathogenesis of HS, we hypothesize:

1) Patients with HS will have a higher prevalence of anemia as compared to the general population.
2) Patients with a higher Hurley Stage are more likely to develop anemia compared to patients with a lower Hurley stage.

Methods

The study is being reported in accordance with the STROBE guidelines. This study has been approved by the international review board (IRB) at McGill University. We conducted a retrospective case series of 128 HS patients seen at the Montreal General Hospital from 2015- 2019. We included all HS patients, over the age of 18, who had blood tests done within one year of diagnosis at our clinic (1 year before and/or after diagnosis). We reviewed the patient's charts and collected information about patient age, sex, ethnicity, smoking status, diabetes, hypertension and other inflammatory conditions. We also collected data on the date of diagnosis by our clinic. The Hurley staging at the time of diagnosis was recorded. Blood tests done within 1 year of diagnosis were included and blood test results that were collected included hemoglobin, mean corpuscular volume (MCV) and hematocrit. In the event the patient had multiple blood test results within the included time period, if anemia was recorded at any time, the value closest to the time of diagnosis was included. If there was no anemia, the value closest to the time of diagnosis was included. Anemia was defined as Hgb <130mg/dL in males and <120mg/dL in females and normal ranges at the Montreal general hospital range from 130-180 mg/dL for males and 120-160mg/dL for females

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The association between anemia and the variables collected was assessed via univariate logistic regression. Significant associations ($p < 0.05$) were included in a multivariate logistic regression model.

Results

One hundred and four patients were included in the study. Table 1 outlines the demographics of our patient population. Fifty-nine patients (56.7%) were male and 45 (43.3%) were female. The mean age was 39.9 years with males on average being 41.8 years old and females being 38.5 years old. Ninety patients (86.5%) did not have diabetes and majority of the patients were nonsmokers (59.6%). Only 12 (11.5%) of the patients had hypertension. There was a relatively similar distribution of patients from each Hurley stage. Thirty-two patients (30.8%) were Hurley stage I, 38 patients (36.5%) were Hurley stage II and 34 patients (32.7%) were Hurley stage III. 62 patients (59.6%) were Caucasian, 12 patients (11.5%) were African Canadian, and 30 patients (28.9%) were of other ethnic origins.

Table 2 outlines the hematological parameters of our patient population. Thirty patients (28.9%) in the sample had anemia. The mean hemoglobin level for the entire cohort population was 132.4g/L with a range of 62-169g/L. Males had a higher mean hemoglobin (138.3 g/L), compared to females (127.8 g/L), as expected. The mean hemoglobin for males in Hurley stage I was 147.8 g/L and for females was 133.0 g/L. Male patients with Hurley stage II had a mean hemoglobin of 139.6 g/L and females had a mean hemoglobin on 125.9 g/L. Males in Hurley stage III had a mean hemoglobin of 133.2 g/L and females had a mean hemoglobin of 122.6 g/L. The mean corpuscular volume (MCV)

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in males with anemia was 83.22fl and 83.1fl for females. The mean hematocrit level was 0.42 for males and. 0.39 for females.

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Table 3 outlines the results of our univariate regression analysis. On univariate regression analysis, having diabetes OR 4.12 95% CI [1.28, 13.18] and being of African origin OR 4.03 95% CI [1.11, 14.49] were found to be associated with increased odds of developing anemia. When diabetes and ethnicity were controlled for on multivariate analysis, patients with Hurley II and Hurley III had increased odds of developing anemia compared to Hurley I (OR 7.56 95%CI [1.39,40.89], and OR 12.62 95%CI [2.24,71.15], respectively).

Discussion

Our findings suggest an association between HS and anemia. Approximately 30% of patients in our sample had anemia which is in line with the literature which ranges from 18.63%[67] to 43% [65]. The prevalence of anemia in our population was higher than the general population which is reported at approximately 5.6% in the United States[68]. When risk factors were controlled for, the severity of disease correlated with the risk of developing anemia. Severity of chronic inflammatory states has been shown to correlates with elevation in inflammatory cytokines. *Jiminez Galo et al*. concluded that the higher levels of IL-6, c-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) correlated with the degree of disease severity based on HS-PGA scores[69]. In our study, patients with Hurley III had higher odds of developing anemia compared to Hurley I and Hurley II. This finding is consistent with those made by *Kimball et al*. *Soliman et al and Seyed et al*. [55, 64, 70] .

In our study, diabetic patients were also found to have higher risk of developing anemia. Diabetes is a chronic condition that is signified by insulin resistance and decreased insulin levels. Additionally, an increased inflammatory response is frequently seen in diabetics and these patients have been found to have increased levels of IL-1, IL6, TNF alpha, CRP and ESR[71]. The role of inflammation in the pathogenesis of anemia and the elevated inflammatory markers support our finding of increased anemia in our diabetic population of HS patients. Additionally, dietary habits combined with decreased gastric absorption due to diabetic complications such as gastroparesis may also play a role in anemia in diabetic patients.

African origin HS patients in our population were also found to have higher odds of developing anemia. African origin patients are known to have more severe HS as compared to non-African origin patients. One retrospective single-center study reported that African American patients accounted for 48.2% of HS patients with Hurley III and African American patients were 2.5 times more likely to have Hurley II/III disease than non-African American patients[72]. More severe disease in this patient population could be one of the factors accounting for the higher rates of anemia noted in this population in our study. Additionally, it is apparent that the average hemoglobin and hematocrit levels, white blood cell count and absolute granulocyte count, and TS are lower in the African-American than in the white group, and that the serum ferritin and absolute lymphocyte count is higher in the African-American group[73]. On average, hemoglobin levels are 0.7g/dL lower for both African-American males and females compared to Caucasians[74], confounding our results to some degree.

The limitations of this study include a small sample size. The absence of a control group, which is difficult to create in such a study, also leads to possible confounding of the results. Lastly, this study was conducted in North America, and hence the generalizability of the results may be limited.

In conclusion, patients with HS have a higher prevalence of anemia compared to the general population. Having diabetes and being of African origin are risk factors for the development of anemia, hence these factors should be screened for in patients with HS.

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Tables:

Total	104
Male	59 (56.7%)
Female	45 (43.3%)
Age mean, (range) in years	
Sample	39.9, SD 15.1, (18 - 81)
Males	41.8, SD 16.8, (18 - 77)
Females	38.5, SD 13.5, (19 - 81)
Diabetes (number, %)	
Diabetes	14 (13.5%)
No Diabetes	90 (86.5%)
Smoking status (number, %)	
Smoker	42 (40.4%)
Non Smoker/Ex-smoker	62 (59.6%)
Hypertension (number, %)	
Hypertension	12 (11.5%)
No Hypertension	92 (88.5%)
Disease Severity (number, %)	
Hurley I	**32 (30.8%)**
Males	11
Females	21
Hurley II	**38 (36.5%)**
Males	11
Females	27
Hurley III	**34 (32.7%)**
Male	23
Females	11
Ethnicity (number, %)	
Caucasian	62 (59.6%)
African Canadian	12 (11.5%)
Other	30 (28.9%)

Table 1: Patient demographics

Hemoglobin mean, (range) in years		**Normal Range HgB MGH**
Sample	132.4, 19.4 (62 - 169)	
Males	138.3, 19.1 (78 - 169)	130-180mg/dL
Females	127.8, 18.5 (62 - 163)	120-160mg/dL
Hemoglobin mean, SD (range) in years		**Normal Range HgB MGH**
Hurley I		
Males	147.8, 12.3 (128 - 165)	130-180mg/dL
Females	133.0, 10.2 (110 - 155)	120-160mg/dL
Hurley II		
Males	139.5, 16.8 (112 - 169)	
Females	125.9, 18.9 (92 - 163)	
Hurley III		
Males	133.2, 21.3 (78 - 162)	
Females	122.6, 27.3 (62 - 151)	
MCV mean fL, SD, (range) in years		**Normal range MCV MGH**
Sample	87.0, 7.3 (63.3 - 104.9)	
Males	86.6, 7.3 (63.3 - 104.9)	80-100 fL
Females	87.4, 7.3 (66.8 - 98.6)	80-100 fL
HCT mean , SD (range) in years		**Normal range HCT MGH**
Sample	0.40, 0.05 (0.20 - 0.50)	
Males	0.42, 0.05 (0.24 - 0.50)	0.40-0.54
Females	0.39, 0.05 (0.20 - 0.50)	0.36-0.48
Anemia (number, %)		
Sample	30 (28.9%)	
Males	14 (31.1%)	
Females	16 (27.1%)	

Table 2: Hematological parameters.

	OR Anemia	CI 95%	
Age	1.02	0.99 - 1.05	p = 0.130
Sex	1.21	0.52 - 2.85	p = 0.656
Diabetes	***4.12***	***1.28 - 13.18***	***p = 0.017***
Smoking	0.98	0.41 - 2.32	p = 0.959
Disease Severity (number, %)			
Hurley I	**ref**		
Hurley II	**7.80**	**1.61 - 37.89**	***p = 0.011***
Hurley III	**5.67**	**2.43 - 57.69**	***p = 0.002***
Ethnicity			
Caucasian	ref		
African Canadian	**4.03**	**1.11 - 14.49**	
Other	0.88	0.32 - 2.43	

Table 3: Univariate logistical regression for odds of developing anemia

10. Comprehensive scholarly discussion of all study findings

Hidradenitis suppurativa is a chronic follicular occlusive disease characterized by painful nodules, abscesses and draining fistulas most commonly in the axillae, ano-genital and inguinal regions. [75] . It affects 1-4% of the population [76] . Hidradenitis suppurativa is a debilitating disorder with high morbidity and inadequate treatment can lead to persistent cutaneous manifestations including drainage of malodorous purulent discharge, chronic scarring and squamous cell carcinomas[76]. Given the nature of these symptoms, HS patients suffer from extended periods of chronic pain and emotional and psychological distress, severely affecting their quality of life (QOL)[76].

The development of HS is associated with specific genetic background as one third of patients report a family history of HS[77]. Environmental factors such as obesity, smoking and hormonal factors also play a role. A combination of these factors leads to the follicular occlusion which results in increased inflammation with release of cytokines such as IL1, IL4, IL-17 and TNF alpha, leading to follicular inflammation and rupture[77].

HS is known to be associated with several comorbidities. The greater inflammatory load in patients with HS leads to greater cardiac and metabolic comorbidities in this population[78]. The presence of metabolic syndrome in patients with HS has been reported to be up to 50.6%, a number which is significantly higher than the general population[79]. A systematic review and meta-analysis of nine

studies reported that patients with HS had higher rates of triglyceridemia and elevated low-density lipoproteins[80]. *Phan et al*. in 2019 reported that patients with HS had a 1.69-fold increased odds of developing diabetes[33]. As a consequence of elevated metabolic and cardiac risk factors, patients with HS are at increased risk of myocardial infarctions, ischemic strokes and cardiovascular associated mortality[81].

Patients with HS are also at higher risk of endocrinological abnormalities. Hormone dysfunction likely plays a role in the pathogenesis of HS and female patients with HS has a significantly higher prevalence of HS as compared to the general population (9.0% vs 2.9%)[3]. Patients with HS have also been found to have higher rates of hyperthyroidism, however, few studies have explored this association and the quality of these studies is limited[82].

Gastrointestinal comorbidities associated with HS include Crohn's disease and ulcerative colitis. The prevalence of Crohn's disease in HS patients has been reported to be approximately 0.8% vs. 0.3% in the general population[83]. Similarly, the prevalence of ulcerative colitis has been reported to be 1.3% vs 0.3% for the general population[83]. In hospital studies of HS patients have revealed that patients with HS and inflammatory bowel disease (IBD) tend to be younger than in HS patients without IBD[84]. These patients also had a longer hospital stay and greater cost of hospitalization[84]. Cytokines such as TNF- alpha and IL-17 were elevated in both HS and IBD patients and likely play a role in disease pathogenesis [85].

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Axial spondyloarthritis has been found to be more common in HS patients as compared to the general population. A cross-sectional study from the Netherlands reported that in a cohort of patients

with axial spondyloarthritis, 9.1% of patients had HS[86]. Other rheumatological conditions associated with HS include systemic lupus erythematosus, which has been reported in a case report[87].

Other medical comorbidities associated with HS include malignancies such as non-Hodgkin's lymphoma, Hodgkin's lymphoma, cutaneous T cell lymphomas(CTCL) and SCCs[88]. Hidradenitis suppurativa is known to be associated with psychiatric comorbidities as these patients suffer from significant emotional challenges. Patients with HS report a decreased quality of life, increased sexual distress, greater rates of completing suicide and higher rates of anxiety and depression[89].

Although, HS is known to be a systemic inflammatory disease and anemia is known to be a condition associated with inflammation, the association between HS and anemia has not been well studied and the purpose of this study was to determine the association between HS and anemia.

Our retrospective cohort study reported that there was a higher prevalence of anemia in our HS population compared to the general population. Patients with increased disease severity were at higher odds of developing anemia and risk factors for developing anemia in our population included diabetes and being of African origin. The findings of our study urge clinicians to consider hematological investigations for anemia in HS patients and to treat underlying anemia if present.

Our findings suggest an association between HS and anemia. Approximately 30% of patients in our cohort had anemia which is in line with the literature which ranges from 18.63%[67] to 43% [65].

The prevalence of anemia in our population was higher than the general population which is reported at approximately 5.6% in the United States[68].

Chronic inflammatory states lead to increased hepcidin production and increased iron uptake into inflammatory cells. Consequently, less iron is available for erythropoesis, leading to anemia[90]. Chronic inflammatory states also lead to decreased response of erythropoetin in the bone marrow leading to decreased erythropoesis [91]. Although not completely understood, elevated TNF alpha levels in inflammatory conditions, leads to decrease iron uptake by the marrow, leading to anemia[60]. A retrospective study determined that patients with HS were at higher odds of developing iron deficiency anemia, anemia of chronic disease and acute posthemorrhagic anemia[92]. Iron deficiency anemia is characterized by low MCV (<80 fL), low iron, low ferritin, increased transferrin and decreased transferrin saturation[90]. Anemia of chronic disease on the other hand is defined by normal MCV, low iron, low transferrin, low transferrin saturation and normal ferritin[90]. Patients can have a mixed anemia with both iron deficiency anemia and anemia of chronic disease with normal mean corpuscular volume. Therefore, using MCV alone is insufficient to differentiate the types of anemia. It is important to differentiate the types of anemia as the treatment is different for each. Iron deficiency anemia is treated with iron supplementation. Anemia of chronic disease is best treated by addressing the underlying inflammatory condition and with the administration of erythropoetin[93]. In our patient population, the MCV of both males and females was in the normocytic range, however, we did not have sufficient data on iron studies to specify the type of anemia.

Treating anemia can improve patient symptoms and quality of life. Symptoms of anemia include weakness, pallor, fatigue, chills, lethargy, dizziness and fainting[94]. There are no studies about impact of anemia on the quality of life in HS patients, however, when anemia of chronic disease was treated with erythropoetin in patients with chronic kidney disease, a significant portion of treated patients reported increased energy and physical function at 12 weeks, as compared to control subjects[93]. Similarly, rheumatoid arthritis patients who were treated for their anemia of chronic disease, reported decreased number of swollen joints, pain scores and global assessment scores at 6 weeks[95]. When iron deficiency anemia was treated in cancer patients, there was a significant improvement in the quality of life and functional capacities[96].

Being of African origin was a risk factor for the development of anemia in our HS patients. This finding is consistent with the literature as *Jorgesen and Resnik* also report this association [65, 97]. A systematic review conducted in 2021, reported that HS was most common in African Americans, followed by Caucasians and other races[98]. It has been postulated that African Americans have larger and more numerous apocrine glands, resulting in an anatomical predisposition to HS. There may additionally be a genetic component that may be responsible for this association as Chen et al. have reported a possible gamma secretase mutation causing autosomal dominant HS in an African American family[99], however, this mutation can also be found in other ethnic groups. African American patients are also more likely to have more severe disease and it has been reported that black patients have 2.8 times increased odds of developing Hurley stage III disease as compared to their white counterparts[100]. The combination of increased disease severity and genetic predisposition likely explain the increased risk of anemia in patients of African origin.

Our study reported that HS patients with diabetes had higher odds of developing anemia. This finding in supported by the literature. A retrospective cohort study reported that patients with HS and IBD were at increased risk of developing diabetes mellitus and anemia as compared to IBD patients alone[84]. Diabetes is an inflammatory condition with increased levels of IL-1, IL-6, TNF alpha, CRP and ESR[71]. The elevated inflammatory state in both diabetes mellitus and HS likely plays a role in the increased anemia that was identified in this patient population in our study.

Limitations

Our retrospective cohort study is limited by a relatively small sample size. . Additionally, the study was conducted in a North American population, which may not be generalizable to HS patients in other parts of the world. The data collection was done through a manual chart review of handwritten charts, risking the possibility of misinterpreting or missing relevant data points. There exists a risk of unrecognized confounders for anemia, which may not have been accounted for in this study, however, to mitigate that risk we included the most commonly cited risk factors and included them in our analysis. Lastly, although we found an association between anemia and HS, out dataset did not allow for us to determine the type of anemia, which would have important treatment implications.

5. Final conclusion and summary

HS is complex condition which is associated with numerous co-morbities including anemia. It is crucial for physicians to screen for anemia in this patient population and be aware that patients with more severe disease, diabetes and patients of African origin are at higher risk of anemia development.

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