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REVIEW

Hidradenitis Suppurativa Cancer Risk: A Review of the Literature

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Background: This systematic review explores the increased cancer risk in patients with hidradenitis suppurativa (HS), particularly cutaneous squamous cell carcinoma (SCC) and lymphoma. Chronic inflammation and immune dysregulation in HS are identified as key factors contributing to malignant transformation, often observed in areas of prolonged tissue damage.

Objectives and Results: The NOTCH signaling pathway, disrupted by smoking, plays a dual role in cancer, acting as both a tumor suppressor and a proto-oncogene depending on the context. Mutations in NOTCH and TP53 are common in SCC linked to HS, with a prevalence of 0.5% to 4.6%, predominantly in men and localized to the buttock and anogenital regions. Histological analyses suggest that malignant transformation occurs within keratinized epithelium, supported by altered cytokeratin expression. Immune dysregulation in HS-affected areas, compounded by scarring and lymphatic disruption, further exacerbates tumorigenic potential. While anti-TNF-alpha therapies have been implicated in cancer risk, conflicting evidence and meta-analyses suggest no consistent increase in non-melanoma skin cancers (NMSC). Similarly, IL-17 inhibitors show potential risks but lack robust evidence in HS-specific populations.

Conclusion: In conclusion, HS-associated malignancies, particularly SCC, underscore the need for further research to elucidate the mechanisms linking chronic inflammation to cancer development. Insights from such studies could guide preventative and therapeutic strategies, improving outcomes for HS patients.

Keywords: hidradenitis suppurativa, treatment, skin cancer

Introduction

Hidradenitis suppurativa (HS) is a chronic, relapsing inflammatory skin condition that primarily affects the axillary, submammary, genital, inguinal, and perianal areas. Patients with HS typically develop inflammatory nodules, abscesses, sinus tracts, fistulas, scars, and contractures.[1,2] The global prevalence of HS is estimated to be between 0.4% and 1%. Among the Caucasian population, the female-to-male ratio is approximately 3:1.[1,2] The Hurley classification system, widely used to assess the clinical severity of HS, defines stage 1 as transient abscesses without scarring or sinus tracts, stage 2 as recurrent abscesses with the formation of a single sinus tract, and stage 3 as multiple abscesses and fistulas accompanied by extensive scarring.[3,4] Treatment options include topical antiseptics, local and systemic antibiotics, high-dose zinc therapy, intralesional and systemic corticosteroids, dapsone, cyclosporine A, retinoids and surgery. Biologic treatments with Adalimumab, Secukinumab and Bimekizumab provide promising non-surgical approaches for moderate to severe HS.[2,5–8] Additionally, research into the use of other biologics and small molecules is ongoing.[9–11] Nevertheless, a combination of systemic and surgical treatments remains the standard approach for patients with moderate to severe HS and may offer significant benefits. The pathogenesis of HS is still not fully understood, but it is believed to be multifactorial with a genetic predisposition. Mutations in three proteins of the γ-secretase complex are reported in these patients. Presenilins (PSEN), nicastrin (NCSTN), and presenilin enhancer 2 (PSENEN) are defective and absent, so the Notch signaling pathway is not activated. Such defection leads to epidermal hyperplasia, abnormal follicular

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keratinization, and cyst formation.[12] HS is considered a systemic disease, being associated with type II diabetes mellitus, polycystic ovary syndrome (PCOS), metabolic syndrome, obesity, dyslipidemia, hypertension, inflammatory bowel disease, spondyloarthropathy, and psychiatric comorbidities such as depression. In this context, the link between HS and malignancy remains a subject of ongoing debate. However, there is insufficient evidence regarding the incidence of malignancies in patients with HS. Hence, this study seeks to integrate insights into the pathogenesis of HS with a review of the current evidence on the relationship between HS and malignancy.

Methods

Search Strategy

In this systematic review, we conducted a search across PubMed, Medline, and Web of Science in November 2024, adhering to the 2020 PRISMA guidelines.[13] The search terms used were: ("hidradenitis suppurativa" OR "acne inversa") AND ("malignant disease" OR "cancer" OR "carcinoma" OR "neoplasm" OR "neoplasia" OR "skin cancer" OR "melanoma" OR "leukemia" OR "AIDS-related cancers" OR "sarcoma" OR "tumors" OR "lymphoma" OR "metastases" OR "metastasis" OR "mycosis fungoides" OR "sezary-syndrome" OR "chemotherapy" OR "radiation" OR "immunotherapy" OR "tumor surgery" OR "hematological diseases" OR "overall cancer risk" OR "cancer incidence"). We identified 450 relevant articles published between 1978 and 2024; of these, only 52 had the inclusion criteria we had chosen. Figure 1 illustrates the flowchart of the search process.

Eligibility Criteria

Meta-analyses, experimental studies, case-control studies, cross-sectional studies, cohort studies, and recently published case reports and series were included if they were published in English and focused on human populations. Reviews, abstracts, and letters to the editor were excluded from this analysis. Two medical scientists independently screened and selected eligible articles, with a third scientist consulted in cases of uncertainty regarding inclusion or exclusion. Titles and abstracts were initially screened to determine eligibility, followed by a comprehensive review of the full texts to assess the level of evidence based on the study type.

Results

HS and Global Cancer Risk

HS is associated with several comorbidities such as metabolic syndrome, diabetes mellitus type II, PCOS, inflammatory bowel disease and increased risk of cardiovascular disease.[14] This is due to the chronic inflammatory nature of the disease that mainly manifests itself on the skin, but whose altered mechanisms of the immune system are also expressed systemically. This observation can also be applied to other chronic inflammatory skin conditions and even more investigated than HS, such as psoriasis.[15] The relationship between HS and cancer is still debated.These patients are considered to have a higher risk of malignancy than the general population. A 2001 study of the Swedish population estimated a 50% increase in cancer prevalence in a cohort of 2119 patients with HS compared to the general population.[16] The same study established a statistically significant increased risk for non-melanoma skin cancer (NMSC), with standardized incidence ratio (SIR) 4.6, liver cancer (SIR 10.0) and buccal cancer (SIR 5.5).[16] An increased incidence among HS patients had also been observed for other cancers, but not in a statistically significant way.[16] A more recent Korean study compared a population of 22468 hS patients with 179,734 matched controls and established a higher risk of cancer occurrence among HS patients, with an adjusted hazard ratio (aHR) of 1.28. Specifically, the most involved malignancies were Hodgkin lymphoma (HL) (aHR 5.08), oral carcinoma (aHR 3.10), central nervous system cancer (aHR 2.40), and NMSC (aHR2.06).[17] Cancer risk was increased in both HS patients aged <40 years (aHR 1.34) and those ≥40 years (aHR 1.26), while among women with HS there were no statistically significant differences with controls (aHR 1.16), unlike affected men who showed aHR 1.37.[17]

Certainly, a common risk factor between HS and cancer is recognized. Smoking is more frequent in HS than controls. Cigarette smoking, in fact, promotes the increase of Tumor Necrosis Factor α (TNFα) and other inflammatory cytokines implicated in the onset of HS and stimulates keratinocytes differentiation and growth through nicotinic receptors present

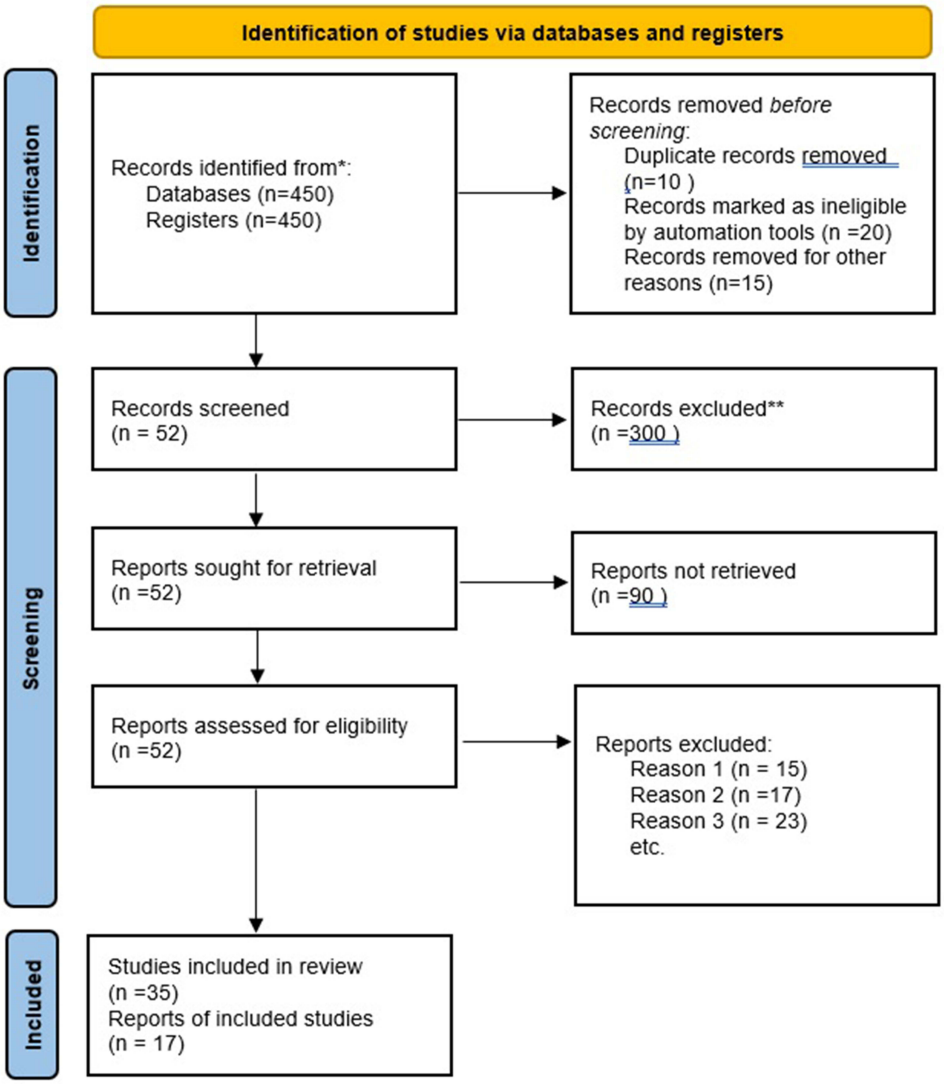

Figure 1 PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only.
Notes: *Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers). **If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

in sweat glands, resulting in infundibular hyperkeratosis.[18] On the other hand, smoking is widely recognized as one of the major risk factors for cancer occurrence in various body districts and is estimated to be responsible for one third of cancer deaths.[19] Considering that tobacco smokers' rate is higher among patients with HS,[20] it is clear that this also affects from a malignancy perspective. The relationship between alcohol and HS is controversial. Although a study by Walter et al observes a slightly increased risk of HS recurrence among alcohol users in surgically treated HS patients, in the literature mostly alcoholism has no statistically significant impact on this condition.[21] The role of diet toward HS is also under investigation. Poor dietary habits can induce increased body mass index, with obesity being a recognized risk factor for HS.[21]

HS and Skin Malignancies

Starting with the district that HS most involves, the skin can be affected by two types of malignancy, melanoma and NMSC. Regarding the former, there are no reported cross-sectional studies or cohort studies showing a positive association between HS and melanoma,[22] except for a recent work by Brydges et al. They carried out a cross-sectional study on 180 million US patients and observed, through odds ratios, that among black patients with HS

there was a positive association with melanoma (OR 2.39) and basal cell carcinoma (BCC, OR 2.69).[23] However, the latter is not the most frequent NMSC type associated with HS. Transformation of chronic HS lesion to squamous cell carcinoma (SCC) is considered the most dreaded complication of HS, and its prevalence stands at 4.6% of HS patients, more frequent in men.[24] In addition to the chronic inflammation underlying HS lesions, the most widely considered risk factors for the transformation of these lesions into SCC are smoking and human papilloma virus (HPV).[24] Of the former we have already mentioned earlier, and it should also be remembered that it causes downregulation of the NOTCH signaling pathway, which is already impaired in HS patients. Under normal conditions, NOTCH is a suppressor of SCC; hence as a consequence, patients with HS, especially smokers are more susceptible to the onset of SCC.[25] Lavogiez et al analyzed 13 cases of squamous cell carcinoma complicating HS, and 7 out of 13 were well-differentiated carcinomas in which high-risk HPV-16 and various subgroups of beta-HPV were found.[26] Gierek et al analyzed 74 patients with HS and SCC. Again, men were more commonly affected (85.1%) than women. The mean age of the patients was 52.67 years, while the mean duration of HS was 25.79 years.[27] Almost all patients had SCC in the gluteal/perianal region (94.6%) and it manifested as a tumor in 61.1% of cases, as an ulcer in 36.1% of cases, and as a nodule in the remaining 2.8%.[27] Thus, it must be kept in mind that SCC can manifest clinically in a heterogeneous way and is not always easy to distinguish from chronic HS lesions. In addition, Marjolin ulcer development, as described in the case report of Katz et al, may be possible. They described the case of a 61-year-old patient with a history of more than 20 years of HS of the buttocks developed a rapidly enlarging ulcer. Biopsy was required, and histologic examination confirmed the diagnosis of SCC.[28] The authors report no significant differences between Marjolin ulcer and a "normal" SCC.

Not only SCCs may arise on HS lesions, but rarer cases of mucinous adenocarcinoma are reported in these patients, particularly of the perianal, perineal, and gluteal region. This tumor constitutes only 2–3% of gastrointestinal malignancies and often mimics the lesions of HS and Crohn's disease, to which it often follows.[29] Nasir et al described the case of a 53-year-old male patient with a 10-year history of perianal HS. The patient was following therapy with adalimumab and antibiotics and had undergone several surgeries for incision and drainage of perianal abscesses. A perianal fistula was also present and treated several times with draining setons. Given the persistence of the manifestations and after magnetic resonance imaging, surgical treatment was chosen and biopsy was performed, from the histological examination of which a mucinous adenocarcinoma classified pT3 was detected.[29] In addition, Kim et al described the case of a 62-year-old male patient suffering from HS with recurrent abscesses in the buttocks for about 3 years. Despite several treatments, the persistence of the manifestations necessitated evaluation with computed tomography and positron emission tomography, which showed a 10-cm-long abscess and increased uptake of fluorodeoxyglucose in the buttocks and at the perianal level. Surgery was then performed, and by histopathological evaluation, a diagnosis of mucinous adenocarcinoma of the buttocks was obtained.[30] A case of perianal mucinous adenocarcinoma was also reported in a 48-year-old woman who had suffered from vulvar and perianal HS for 10 years.[31]

HS and Female Neoplasms

A review by Makris et al analyzed 7 studies that included 9 patients with HS and vulvar carcinoma. The mean age of these patients was 53.5 years, and all but one had HS for at least 15 years with Hurley stage at least II. Advanced grade SCC was discovered in all cases except for two T1N0M0 SCCs, including one from the patient with more recent HS (2 years) and Hurley stage I.[32] Rastogi et al conducted a study of the Midwestern US female population, comparing data from 716 patients with HS with 13,3220 controls extrapolated from the records of the and Northwestern University dermatology clinic from January 2001 to October 2017. Among the controls, 142 anogenital cancers were found, while 3 patients with HS (in all groin was involved) were diagnosed with vulvar cancer (adjusted OR 5.56). Notably, the incidence of vulvar cancer among patients without HS was 0.3 per 10,000 persons per year, while among patients with HS it was 2.6 per 10,000 persons for year.[33] It is worth noting that cases of malignancy in conjunction with HS are not limited to the genital area. Cohen-Kurzrock and Riahi described the case of a 30-year-old woman with draining lesions and wounds between and on the breasts, armpits, and groin for about 7 months, establishing a diagnosis of HS. On clinical examination they also noted a 4-centimeter lump in the right breast. Antibiotic therapy with minocycline 100 mg and topical clindamycin 1% was prescribed. At the follow-up visit after 3 months, the patient was in good condition except for the right breast lump, which was found to have increased in size. A skin biopsy was then performed in

suspicion of malignancy, which was confirmed by histological examination for adenocarcinoma of the breast. The authors do not question whether chronic HS inflammation caused the onset of the tumor, but they draw attention to the differential diagnosis of certain malignancies that may be underestimated in the context of HS.[34] Specifically, in the case of breast cancer, in 6–10% of cases it may first manifest with nonspecific skin signs such as edema, ulceration, nodules, or, in cases of inflammatory cancer, indurated, sore, and erythematous skin, all of which may also be attributable to HS.[35]

HS and Hematologic Malignancies

Another association investigated is the one between HS and hematologic malignancies. As mentioned earlier, the study by Jung et al found among patients with HS an aHR of 5.08 for HL.[17] This risk is significantly higher for moderate to severe HS (aHR 13.28) than for the mild form (aHR 3.89). In addition, in patients aged ≥40 years the aHR increased to 9.04 compared with age-matched controls.[17] A cross-sectional cohort analysis of 27 integrated health systems across the United States identified 62690 patients with HS and compared them with more than 28 million controls to investigate the prevalence of HL and non-Hodgkin lymphoma (NHL) among patients with HS.The prevalence of HL among HS patients was 0.17%, while among controls 0.09%, with OR 2.21, while for NHL the prevalence was 0.40% and 0.35% respectively, with OR 2.00.[36] Specifically, comparing for NHL across age groups, it was observed that the odds for patients with HS and age 18–44 were 3.64 times higher than for age-matched controls.In particular, comparing by NHL the various age groups, it was observed that the odds for patients with HS and age 18–44 were 3.64 times higher than for equal-age controls, while also in the HS group with ages 45–64 and≥65 the odds were increased compared with controls.[36] The authors conclude that patients with HS have a 2–4 times greater risk of developing lymphomas than the healthy population.[36] This finding is confirmed by Shlyankevich et al with a retrospective case-control study of patients at Massachusetts General Hospital during 1980–2013. Lymphoma was diagnosed in 2% of 1730 hS cases, in contrast to 0.5% in the control group (OR 3.60).[37] Craig and Wen also reported the case of an 18-year-old female patient with HS who had been treated with adalimumab for 4 months and was experiencing back pain. Subsequent investigations showed a destructive lesion of the T12 vertebra that was excised. Histological examination showed the picture of ALK-positive anaplastic large cell lymphoma (ALCL), a rare and aggressive lymphoma (3% of NHLs).[38] Vellaichamy et al also reported the case of a female patient who at age 23 had started adalimumab therapy every 2 weeks for psoriasis with benefit. By 25 years of age, she had developed HS Hurley stage III in armpits and stage II in groin for which adalimumab was increased to every week. At age 26, a lymph node biopsy was performed because of the onset of persistent unexplained inguinal lymphadenopathy and fever associated with nausea, vomiting, and abdominal pain. Histological examination indicated the presence of T-cell/histiocyte-rich large B-cell lymphoma, and adalimumab therapy was discontinued to begin chemotherapy.[39] In light of these reports, the question arises whether the use of adalimumab in the context of HS may further increase the risk of cancer, compared with other inflammatory diseases against which this drug is used. Frew et al in this regard performed a reanalysis of data from 3 studies on the use of adalimumab 40 mg per week for HS, including 591 patients. They compared the incidence rates (IR) of malignancies in these patients, with those of patients using adalimumab for other inflammatory diseases. The rates were higher in the group of patients with HS, comparable only among patients with ankylosing spondylitis, but this increase was not statistically significant. The authors therefore speculate that the higher incidence of malignancy is probably due to the mechanisms underlying HS rather than the action of adalimumab.[40]

Regarding leukemia there is a lack of available data. Jung et al found that patients with HS and age <40 years had higher risk of leukemia than age-matched controls (aHR2.55).[17] In the other hand, Sotoodian et al reported 2 cases of leukemia and who had subsequently developed HS. In the first case a 61-year-old man with hairy cell leukemia developed HS a few months after rituximab treatment, while in the second case a man had been diagnosed with chronic lymphatic leukemia at age 40 and developed HS at age 49.[41] Conversely, Chen et al reported 8 cases of acute myeloid leukemia (AML) arising in patients with HS. The mean age of onset of HS was 23 years, while it was 42 years for AML. In 7 of 8 cases, the diagnosis of AML had been obtained within 4 weeks of worsening HS. For 4 patients, description of HS severity during chemotherapy was available. In 2 of these, HS improved with induction of chemotherapy despite resistance to oral antibiotics, while in 2 others HS worsened. The authors therefore suggest that HS flares can be observed during AML, but that neutrophils are probably not involved in this process as they are low or absent.[42]

HS and Other Malignant Tumors

Regarding other malignancies, several studies have attempted to describe their relationship to HS. A meta-analysis by Bailey et al did not describe a significant increase in malignancy in patients with HS except for pharyngeal and oral cancer.[43] Also, according to Lapins et al the incidence of this type of cancer was increased in patients with HS (aHR 3.10).[16] Jung et al confirmed this finding for both male (aHR 2.80) and female (aHR3.95) patients.[17] A Danish retrospective register-based study of patients diagnosed with HS between 1977–2017 also found SIR 2.3 for oral and pharyngeal cancer.[44] The same work stated that statistically significant increase in incidence in HS population is observed for digestive organs and peritoneum (SIR 1.6), respiratory system (SIR 2.4), urinary tract (SIR 1.5) and lymphatic tissues (SIR 1.5).[44] More specifically, Jung et al found an increased risk of colorectal cancer in the female population with HS (aHR 1.79) and among patients aged ≥40 years (aHR 1.41).[17] The same study described an increased risk of central nervous system malignancy among patients with HS (aHR 3.14), particularly among patients aged <40 years compared with age-matched controls (aHR3.05).[17] Similarly, prostate cancer was also at higher risk among patients with HS (aHR 2.05) and among those with age ≥40 years (aHR 2.05).[17]

Discussion

Our systematic review suggests that patients with HS may have an increased risk of cancer compared with the general population. Several studies have demonstrated a higher incidence of cancer particularly among smokers.

Jourabchi et al proposed that smoking negatively impacts the NOTCH signaling pathway in individuals with HS.[25] Disruption of this pathway interferes with hair follicle homeostasis, leading to follicle rupture and triggering a localized inflammatory reaction.[45] Studies analyzing mRNA and protein expression have identified elevated levels of NOTCH pathway components in HS.[46] In the context of cancer, NOTCH has been found to both promote and inhibit tumor development.[25,45,46] Components of the NOTCH pathway exhibit oncogenic roles and are frequently overexpressed in multiple cancer types, such as acute and chronic lymphocytic leukemias,[47] colorectal cancers,[48] gliomas,[49] and prostate cancers,[50] all of which occur more commonly in HS patients.

In SCC, NOTCH primarily acts as a tumor suppressor;[25,45–47] however, mutations in NOTCH receptors have been identified in SCC, leading to their dysfunction or reduced expression.[51] These mutations are present in both HPV-positive and HPV-negative vulvovaginal SCCs, with HPV-independent cases often involving loss-of-function mutations in NOTCH-1 and TP53, a known tumor suppressor gene.[52] In head and neck cancers, NOTCH-1 mutations point to its role as a tumor suppressor, while activation of the NOTCH pathway suggests a proto-oncogenic potential.[51,52] The overexpression of NOTCH components in HS may exacerbate mutation rates, heightening the likelihood of carcinogenic processes, particularly in the development of SCC linked to HS.

The analyzed articles provide detailed information on the incidence of cutaneous SCC in lesions resulting from chronic HS. The estimated prevalence of this complication ranges from 0.5% to 4.6%.[34] Interestingly, although HS is more prevalent in women, nearly all studies, with one exception, reported a higher occurrence of SCC in men.[34–37] Research indicates that SCC is more frequently observed in the buttock, gluteal, and anogenital regions affected by HS.[53,54] To date, no cases have been documented in the axillary region.

The pathogenesis of SCC in the context of chronic inflammation differs from that associated with prolonged sun exposure, though the exact mechanisms remain unknown. Kurokawa et al identified an infundibular-like keratinized epithelium (type A) in several cases of SCC arising from HS.[55] Histological findings support the hypothesis of malignant transformation within type A epithelium, as indicated by increased levels of undifferentiated cytokeratin (CK14), the expression of simple epithelial keratins (CK7, CK8, CK18, and CK19), and a decrease in stratified and differentiated cytokeratins (CK1 and CK10).[55]

Fabbrocini et al suggested that an "immunocompromised cutaneous area" with weakened immune regulation could account for malignant transformation or susceptibility to infections due to immune dysfunction.[56] In HS, immune dysregulation is evident in affected areas, where scarring disrupts lymphatic microcirculation and peripheral nerve endings. This disruption impairs interactions between lymphocyte-derived immune cells and peripheral nerve neurotransmitters. The destabilization of this relationship may create an environment conducive to tumor development.

There is ongoing debate in the scientific literature regarding the effect of anti-TNF-alpha therapy on the incidence of NMSC and lymphomas. Case reports have documented an association between anti-TNF-alpha treatment and increased cancer risk, suggesting that TNF-α, a pivotal cytokine within the tumor microenvironment, may facilitate tumor progression.[57] Conversely, the inhibition of TNF-α could compromise antitumor immune responses, thereby promoting the growth of immunogenic tumors.[58]

However, TNF-α also plays a critical role in tumor cell eradication mediated by natural killer (NK) cells and CD8+ cytotoxic T lymphocytes.[59,60] This underscores the involvement of TNF-α receptors in tumor immunosurveillance.[61]

According to a meta-analysis of observational studies on the incidence of skin cancers in patients with psoriasis, psoriatic arthritis, and HS treated with biologic therapies, no increased incidence of NMSC or melanoma was found compared to those receiving non-biologic treatments.[57–61]

In conclusion, the conflicting findings underscore the need for further research to clarify the role of TNF-α inhibitors in tumor development. IL-17 inhibitors, another class of biologics approved for the treatment of moderate-to-severe HS and already being used for psoriasis,[62,63] have also been investigated. A meta-analysis by Bilal et al reported an increased cancer risk in rheumatic patients treated with IL inhibitors.[64] However, as IL-17 inhibitors have only recently been introduced for HS treatment and no cancer cases have been reported thus far, it is premature to determine whether these findings can be applied to HS patients.[65–68] Future studies will let us know whether indeed these drugs may play a role in cancer development, but for now there are only case reports or small studies while meta-analyses as reported reassure us on this topic. In this regard, Song et al showed that in mice defective of the Notch ligand Jagged-1 (Jag1), they exhibited epidermal and follicular hyperkeratosis associated with expansion of IL-17a-producing T cells[69] Referring back to the previous discussion, this suggests a possible connection between chronic inflammation, Notch dysfunction, and SCC development. Another important challenge with studies exploring the association between HS and cancer risk is the possibility of ascertainment bias (eg, patients with HS may have an increased risk of skin cancer simply because they are following more closely with dermatology or because they have increase contact with the healthcare system).[70–72]

Conclusion

In summary, numerous studies have highlighted an increased incidence of malignancies in patients with HS, with particular emphasis on cutaneous SCC and lymphoma. SCC in the context of HS is considered a multifactorial malignancy that typically arises in areas of chronic inflammation, where prolonged tissue damage and immune dysregulation may contribute to malignant transformation. Despite these findings, there remains a significant gap in experimental research aimed at investigating the specific role of chronic inflammatory conditions, such as HS, in the carcinogenic process.

Further research is needed to better understand the underlying mechanisms by which chronic inflammation in HS might promote tumorigenesis. In particular, the immunological and genetic drivers leading to the development of malignancy in HS patients should be investigated. This research could provide critical insights into the pathways that link chronic inflammation to cancer development and open the door to novel preventative and therapeutic approaches for HS patients. Given the complexity of the disease and the potential implications for cancer risk, a deeper exploration into this area could offer a valuable foundation for future studies, which may ultimately improve clinical outcomes and inform treatment strategies for individuals affected by HS.

Data Sharing Statement

Data are reported in the current study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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