Complications of hidradenitis suppurativa

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Abstract

Hidradenitis suppurativa (HS) is a chronic inflammatory skin disease characterized by recurrent painful nodules and abscesses involving intertriginous areas. Repeated episodes of profound inflammation in HS can lead to a number of complications, causing significant morbidity and decreasing quality of life. Complications of HS may affect the skin alone or may have systemic impact. Cutaneous complications of HS include sinus tracts, fistulae, scarring and contractures, squamous cell carcinoma, and lymphedema. Systemic complications of HS include chronic pain, systemic amyloidosis, and possibly anemia. Preventing disease complications by controlling primary disease is a key component of HS management. Clinicians should be prepared to recognize complications early, as prompt management is necessary to minimize negative impacts.

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Hidradenitis suppurativa (HS) is a chronic inflammatory skin disease characterized by recurrent painful nodules and abscesses involving intertriginous areas. HS commonly starts in young adulthood, follows a chronic, relapsing and remitting course, and impacts patients for many decades. Repeated episodes of profound inflammation in HS can lead to a number of complications in patients who are often otherwise young, active, and healthy. Complications of HS may affect the skin alone or may have systemic impact. In long-standing, poorly controlled HS, complications may be severe, cause significant morbidity, and decrease quality of life. Early recognition and prompt management of complications is crucial in preventing progression and minimizing negative impacts. We review the current literature on diagnosis and management of HS complications.

Cutaneous complications

Sinus tracts and fistulae

In HS, as occluded follicles rupture and then epithelialize, sinus tracts and fistulae are commonly formed. Sinus tracts are subcutaneous tunneling wounds, that can interconnect to form areas of honeycombing under the skin.[1] In addition, fistulae may form between the skin surface and the inside of a tubular organ, or between 2 tubular organs. Anal fistulae and urethrocutaneous fistulae, which are abnormal tracts connecting skin to the anal canal and to urethra, respectively, have been reported in HS patients.[2-5]

Sinus tracts are typically present in patients with moderate to severe HS. In the Hurley HS staging system, the presence and diffuseness of sinus tracts are largely used to clinically define HS disease severity. Sinus tracts are most commonly found in the groin, followed by the axillae.[6] Fistulae, although not as ubiquitous as sinus tracts, are frequently encountered in perianal HS. Anal fistulae are the most common type of fistula encountered in HS patients. In one retrospective study of 43 patients with perianal HS, 37% were affected by anal fistulae.[2] Urethrocutaneous fistulae in HS patients are much more rare, but have been reported.[3-5] Fistulae to the bladder, vagina, rectum, and bowel should be considered as clinical possibilities in HS patients with perineal, buttock, and groin HS involvement.[3,7]

Sinus tracts collect exudative material and bacteria, resulting in foul-smelling and often purulent drainage that is distressing to patients. In contrast, the clinical presentation of fistulae can vary based on location and the communicating organs. Anal fistulae may present with anal skin irritation; constant, throbbing pain that is exacerbated by sitting, moving, coughing, or bowel movements; foul-smelling discharge from the perianal area; pus or blood in bowel movements; and even fecal incontinence in some cases. Urethrocutaneous fistulae may present with urine leakage from a fistulous opening and local skin irritation.[4]

On physical examination, sinus tracts can be identified as visible and palpable subcutaneous tunnels (Figure 1). While conventionally, sinus tracts are diagnosed on physical exam, color Doppler

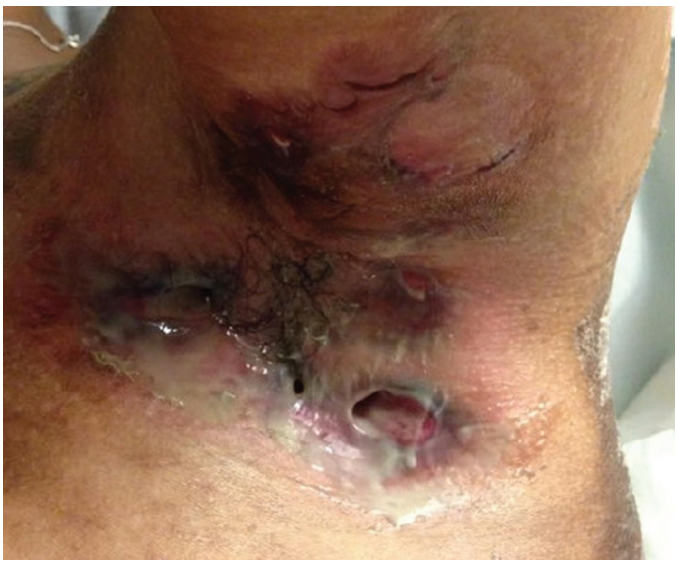

FIGURE 1. Sinus tract formation in hidradenitis suppurativa. Multiple subcutaneous tunnels with purulent drainage are noted in the affected left axilla.

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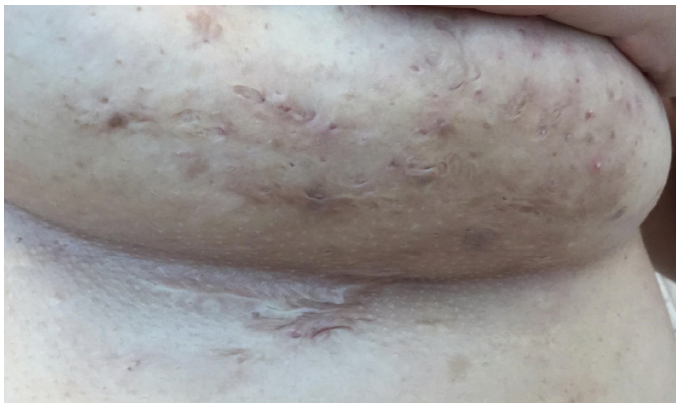

FIGURE 2. Scarring of the inframammary folds in moderate hidradenitis suppurativa (HS). Multiple firm, band-like hypertrophic plaques and smooth, atrophic plaques are present in areas previously affected by HS.

ultrasound has recently been proposed as an adjunctive diagnostic modality. Color Doppler ultrasound may allow for detection of subclinical sinus tracts,[8] and characterization of sinus tract features, such as level of fibrosis and edema.[6] In this way, ultrasound may be useful for grading disease severity and may guide management.[6,8] While both sinus tracts and fistulae present with an opening in the skin and possible drainage, distinguishing one from the other is crucial for guiding management. A fistula should be suspected in the perianal, perineal, or buttock areas when drainage is malodorous, and when symptoms or history are consistent with fistula. To confirm an anal or enterocutaneous fistula and assess its extent, further testing with ultrasound or computed tomography (CT) scan is often indicated.[7] For assessment of a urethral fistula, a retrograde urethrogram may be useful.[3,5]

Prevention of sinus tracts and fistulae is best accomplished with early and aggressive management of HS. Biologic therapies, such as infliximab, may be effective in closing some sinus tracts.[9] However, sinus tracts and fistulae are typically resistant to medical therapies, especially when they are associated with fibrosis.[6] In these cases, surgical management is indicated. At perineal, perianal, and periurethral locations, standard wide local excision with reconstruction can result in fecal or urinary incontinence. Laying open sinus tracts may be considered, especially in areas where radical resection would result in significant morbidity.[10] Similarly, *fistulae* can be unroofed and exteriorized via fistulotomy (ie, by removing all associated granulation tissue and allowing the remaining open wound to heal by secondary intention).[1,11] Fistulae can also be treated by local excision of the individual fistula, termed a *fistulectomy*. HS-associated complex anal fistulae, which include fistulae with multiple tracts, fistulae with more extensive (>30%) involvement of the external anal sphincter, and fistulae with a location high in the anal canal (supra-sphincteric or extra-sphincteric), are more difficult to manage surgically due to the risk of incontinence. A modified seton procedure has been described for the treatment of complex anal fistulae in HS patients.[12] After incision of the external fistula tract, the seton, which is similar to a rubber band, is laid in the tract, tied around the sphincter muscle, and tightened gradually over a period of months. With tightening, the sphincter is slowly transected by the seton, bringing the fistulous tract to the external surface. Ultimately, the seton drops, and the externalized fistulous tract is allowed to heal. This procedure, combined with excision of HS-affected tissue, has been effective for management of complex anal fistulae in HS patients.[12] In some cases, a colostomy may be created to avoid fecal contamination of a perianal surgical wound after excision of HS-affected skin and subcutaneous tissue,[13] or when function of the anal sphincter cannot be preserved. Urethral fistulae as a complication of HS is rarely reported.[3-5] Incision of urethral fistula with a long period of suprapubic urinary diversion, and ileal conduit creation have been discussed as management options in these cases.[3-5]

Scarring and contractures

HS is characterized by waxing and waning periods of chronic inflammation. Repeated episodes of active inflammation are followed by wound healing, leading to significant scar formation in affected areas (Figure 2). Scarring in affected areas may be atrophic or hypertrophic. Atrophic scars present as depressed, smooth, dyspigmented plaques. Hypertrophic scars present as firm, rope-like bands or plaques. Scarring is not only disfiguring, but can also be functionally limiting. In the groin and axillae, contractures may limit range of motion. Scarring in genital and perianal areas can also predispose to rectal, anal, and urethral strictures,[1] resulting in difficulty or pain with defecation or urination. Scarring and subsequent fixation of the anal sphincter can also lead to fecal incontinence.[14] Physical deformity and functional limitations due to scarring should be assessed with thorough history and physical examination of affected areas.

Scarring in HS patients can cause significant embarrassment and emotional distress. Intimate relationships can be affected, and patients' anxiety about their scars may cause them to hide affected areas with clothing and to limit certain behaviors, such as swimming and intimate interactions.[15] In HS patients, the severe negative impact of scars on quality of life has been established, further emphasizing the importance of patient education and management in reducing morbidity.[15] Since scars continue to remodel for a year or more, patients can be counseled that the appearance of recent scars may improve with time, as long as the disease is well-controlled and further inflammation and scarring are minimized. Intralesional kenalog injections can help to soften and improve the appearance of hypertrophic scars. Scars and contractures can be electively treated with surgery to improve their appearance and functional limitation. Scar release, scar excision, and skin grafting are conventional treatments. The use of fractionated carbon dioxide lasers has been successful in treating cosmetically disfiguring and functionally limiting scars in HS patients.[16,17]

Lymphedema and lymphangiectasia

Lymphedema and lymphangiectasia are not an uncommon complication of severe HS involving the genital and perineal areas.[18-23] Chronic inflammation and scarring secondary to HS can cause blockage and destruction of lymphatic channels. With disruption of normal lymphatic drainage, an excess of lymph fluid accumulates in interstitial spaces, leading to lymphedema. Lymphatic obstruction may also result in lymphangiectasia, a proximal saccular dilation of superficial lymphatic vessels.

Lymphedema in HS presents with generalized swelling and widespread indurated plaques as lymph fluid accumulates in a specific region. With the progression of lymphedema, localized

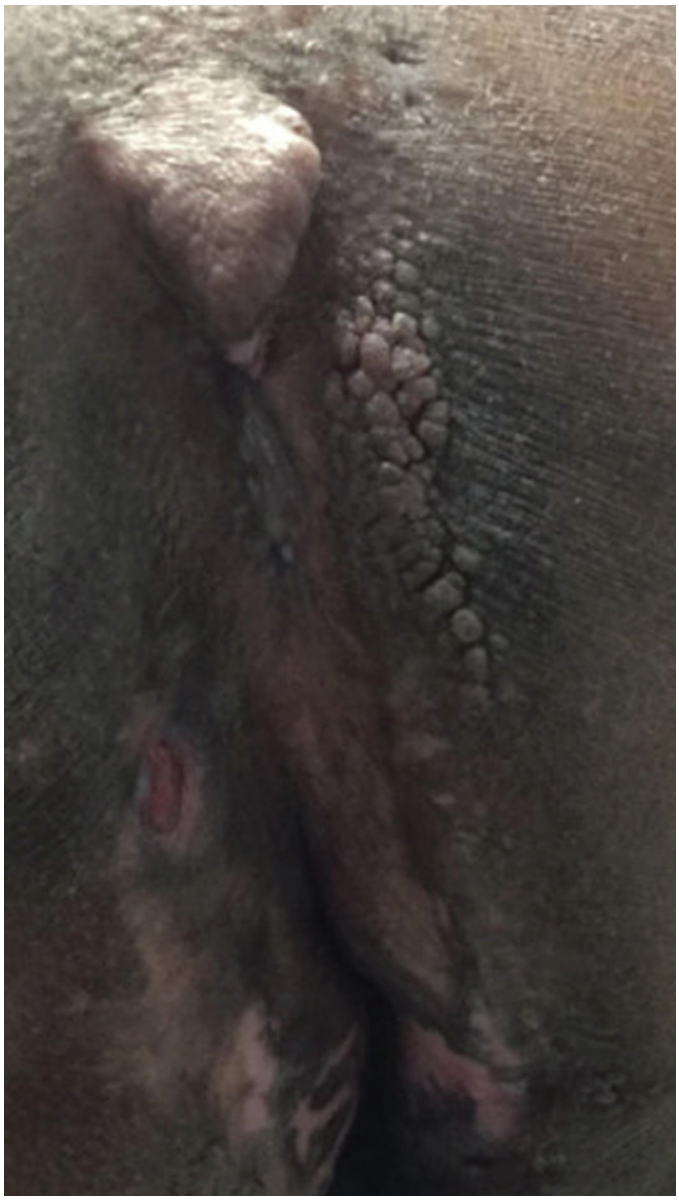

FIGURE 3. Lymphedema and verrucous changes of the buttock and gluteal cleft in severe hidradenitis suppurativa. Generalized swelling of the buttock with large indurated plaques and clustered verrucous papules are observed along the medial buttock and gluteal cleft. In addition, a localized indurated, smooth pedunculated plaque is present at the superior aspect of the gluteal cleft.

verrucous papules and nodules may occur (Figure 3).[24] Lymphangiectasia in HS may present as persistent clusters of clear vesicles, on a base of thickened, woody indurated scrotal and groin skin.[23] Lymphedema in HS has been reported in the groin and buttock areas,[18-24] and there has been one report of abdominal lymphedema secondary to HS of the groin.[24] Theoretically, lymphedema secondary to HS may affect other areas, such as the upper extremities, but this has not been reported. In severe HS involving the perineum and genitals, 5 cases of severe, end-stage lymphedema, or elephantiasis, have been reported in the literature.[18-22] In men, scrotal elephantiasis can present as a firm, massively enlarged, edematous scrotum, in the setting of perineal induration and scarring secondary to HS.[18-20] Penile lymphedema from perineal fibrosis secondary to chronic HS, without scrotal involvement, has also been described.[21] In women, lymphedema and lymphangiectasia can present as significant enlargement and firmness of the mons pubis and labia majora in the setting of chronic HS.[22]

Lymphedema and lymphangiectasia can generally be diagnosed by characteristic physical examination findings. Verrucous lymphostasis changes may be clinically indistinguishable from SCC or verrucous carcinoma,[24] so a low threshold for diagnostic biopsy should be exercised to rule out underlying malignancy in clinically suspicious lesions. Depending on the clinical extent of lymphedema, imaging with CT or MRI may be appropriate, particularly preoperatively to avoid inadvertent injury to vital structures. As lymphedema and fibrosis distorts normal anatomy and architecture, imaging can help in evaluating for fistulas, urethral involvement, testicular involvement, or underlying malignancy.[18-22]

Lymphedema is typically first managed conservatively with compression garments and physical decompression.[24] Anogenital lymphedema may be particularly difficult to treat conservatively, and verrucous lymphostasis changes may not respond to medical therapies.[24] If lymphedema is severe, patients may be referred for surgical excision of affected areas, followed by coverage of the resulting wound with split-thickness skin graft or a local flap.[18,20,21] Healing by secondary intention after surgical excision may be considered in some cases.[18] Carbon dioxide laser excision of lymphedematous scrotal skin, with secondary intention healing, has also been reported to be successful, with no recurrence at 18-month follow-up.[23]

Squamous cell carcinoma

Malignant degeneration of chronically inflamed tissue is known to occur in chronic wounds. Years of recurrent inflammation in severe HS has been reported to contribute to development of cutaneous malignancies, including squamous cell carcinoma (SCC)[14,25-53] and verrucous carcinoma,[54] at affected sites.[25] These malignancies arising from chronic HS have been noted to occur exclusively in the groin and buttock areas, leading to interest in whether human papillomavirus (HPV) infection at these sites plays a role in pathogenesis. In a series of 8 SCCs arising in HS, polymerase chain reaction (PCR) demonstrated the presence of HPV in all samples, predominantly high-risk HPV-16.[54] HPV-16 has been previously implicated in the development of cervical cancer, and associated with nonmelanoma skin cancer in nonimmunosuppressed patients.[55] While more studies are needed, these data implicate HPV as a possible viral cofactor in the pathogenesis of HS-related SCC and verrucous carcinoma.[54] It has also been suggested that reduced defensins and impaired NOTCH signaling in severe HS may contribute to development of SCC in severe HS.[56]

SCC has been described in chronic, uncontrolled HS. In a 7-year retrospective review of 72 HS patients who underwent surgery for HS, the reported prevalence of SCC was 2.78%.[25] In a separate review of 217 HS patients, SCC prevalence was 4.6%.[54] The average age of patients with HS-related SCC was 51 years in a review of 86 cases in the literature.[57] Although women are more likely to be affected by HS, SCC in the context of HS occurs much more commonly in men, with an observed male-to-female ratio of 4:1 upon review of 30 published cases.[28]

SCC presents as a late complication of HS. It is reported, on

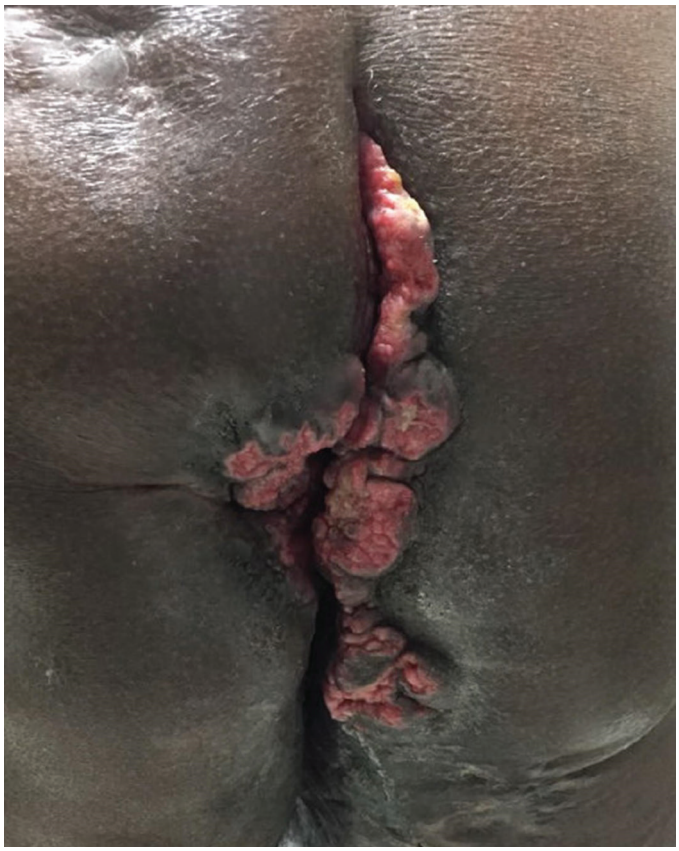

FIGURE 4. Invasive squamous cell carcinoma of the gluteal cleft in long-standing hidradenitis suppurativa. An exophytic, friable, pink tumor involves the bilateral medial buttocks and gluteal cleft.

average, after 16-32 years of refractory HS,[34] although presentation as early as after 3 years of active HS has been reported.[47] SCC often presents as exophytic, friable masses with everted edges, and verrucous carcinoma usually presents with verrucous skin changes. However, SCC in the context of HS may not present with these features.[25] The presentation may be a nonhealing or slowly enlarging ulcer, or local pain.[58] SCC in chronic HS has only been reported in genital, perianal, perineal, inguinal, and buttock areas (Figure 4).[57] HS-associated SCC is reported to have an aggressive nature, high metastatic potential, and poor prognosis. Mortality from HS-related SCC has been estimated at 48% within 2 years of diagnosis,[28] and 42.9% in a more recent review of 21 cases in the literature.[57]

Given the aggressive nature and poor prognosis of HS-associated SCC, early diagnosis and management of SCC is crucial. A high index of suspicion for SCC should be exercised in the setting of rapidly growing friable tumor mass, new skin changes, nonhealing ulcer, or increased pain in chronically-diseased areas.[34,57] As malignant degeneration in chronic wounds is usually a focal process, and does not involve the entire wound, there is significant risk of false-negative biopsies.[58] If clinical suspicion is high for malignancy, wide local excision of the entire lesion to subcutaneous tissue should be performed for diagnostic evaluation.

For any patient with suspected or biopsy-confirmed SCC, thorough evaluation for lymph node metastasis is advised, including clinical examination and possibly imaging to fully confirm the extent of disease preoperatively.[59] For localized and operable SCCs, a margin of at least 2 cm has been suggested.[54] Sentinel lymph node biopsy at the time of surgical excision has also been advocated to definitively rule out lymph node involvement.[54] For HS-associated metastatic SCC, management should be multidisciplinary, with involvement of surgical oncology, medical oncology, and radiation oncology.[25] Unfortunately, due to the aggressive nature of HS-related SCC, recurrence and metastasis after wide local excision is not uncommon.[54]

Systemic complications

Chronic pain

The typical lesions of active HS can cause significant pain, given both their inflammatory nature and their location in intertriginous and sensitive areas. Secondary bacterial colonization of lesions may further exacerbate pain. Firm scars and contractures can cause discomfort and pain with movement.

HS patients report significant chronic pain associated with HS in studies examining health-related quality of life.[15,60-62] These studies ranged in size from 12 to 160 subjects, and utilized interviews[15] and validated quality-of-life surveys[15,60-62] to assess impact of pain on quality of life. A retrospective review of 283 HS patients (45.9% Hurley stage I, 35.3% Hurley stage II) found that 39.9% of HS patients were formally diagnosed with chronic pain,[63] and women were twice as likely as men to report chronic pain.[63] HS-associated pain correlates with disease severity and depression, causes emotional distress, and significantly impacts quality of life.[15,60-63] Pain also often limits daily activities, work, and relationships.[15] A complete history and physical examination allows the physician to determine the intensity of HS-associated pain and its effect on a patient's quality of life, and can help guide multidisciplinary management.

The management of chronic pain in HS involves treatment and control of the primary disease first and foremost. In addition to management of active inflammatory disease, long-term pain management is frequently warranted in patients with moderate to severe HS.[64,65] Choice and dosing of pain medication should include consideration of comorbidities, such as advanced age and hepatic, renal, or cardiovascular disease. First-line pain management generally involves nonopioids, such as acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs). In patients with a history of peptic ulcer and/or active glucocorticoid use, NSAIDs should be used with caution. For pain that is more severe and refractory to first-line nonopioids, opioid therapy may be an option. For sustained pain, transition from short-acting opioids to a regimen of long-acting opioids, dosed 2 or 3 times daily, with short-acting opioids for breakthrough pain, is advisable. Opioid rotation is a strategy that may be effective for patients who have developed tolerance to a certain agent, or for patients who do not tolerate adverse effects of a specific agent.[64] Choice of therapeutic agent and dosing may also depend on current and previous pain regimens. For example, chronic opioid use leads to tolerance, such that higher doses are often required to achieve analgesic effect. As pain management in HS patients can be extremely complex, coordination of care with a pain specialist is advisable.[64]

As with pain management for other chronic disorders, the potential for nonadherence to the prescribed regimen, as well as risk of opioid addiction and substance abuse, should be continually assessed and monitored.[64] At the same time, it is important to accurately assess

pain in HS patients and treat accordingly given the known impact of pain on quality of life in this patient population.[15,60-62]

Systemic amyloidosis and nephrotic syndrome

The chronic inflammation of HS has been associated with systemic increase in acute phase protein amyloid A. Excess amyloid proteins clump together and deposit in tissues, thereby disrupting the normal function of affected organs in a condition known as *systemic amyloidosis*.[66,67] The kidneys are the first organ to be affected in systemic amyloidosis, as amyloid deposits in renal glomeruli and tubules.[67] Renal amyloid can lead to asymptomatic proteinuria, progressing to nephrotic syndrome, and ultimately to renal failure. The next most common organ to be affected is the heart, but cardiac involvement is rare and usually asymptomatic.[68] Besides HS, secondary systemic amyloidosis also occurs in response to various other chronic inflammatory disorders, including rheumatoid arthritis, psoriatic arthritis, and inflammatory bowel disease.[66]

Secondary systemic amyloidosis associated with HS is extremely rare, with 10 cases of this complication reported in the literature.[66-75] In all cases, patients had long-standing poorly-controlled HS that was refractory to multiple conventional treatments.[66-70,73]

Hidradenitis suppurativa with secondary amyloidosis may present with signs of nephrotic syndrome. Symptoms may include progressive positional edema, periorbital and pretibial edema,[69,70] hypoalbuminemia, and proteinuria.[70] Serum creatinine may be modestly or markedly elevated,[67,70] indicating functional renal impairment from amyloid, or within normal limits.[69] Bilateral pleural effusions may develop secondary to hypoalbuminemia and a decrease in oncotic pressure in pulmonary vasculature.[69]

Diagnosis of proteinuria or nephrotic syndrome can be made by history, physical examination, and laboratory findings. A diagnosis of nephrotic syndrome in the setting of long-standing, poorly controlled HS should prompt consideration and workup for secondary systemic amyloidosis. Definitive diagnosis of renal amyloidosis can only be made with a renal biopsy showing abundant interstitial and vascular amyloid A deposits.[68] In patients with severe, uncontrolled HS, it may be wise to screen for microalbuminuria and serum albumin to avoid delay in diagnosis and progression of this serious complication.[66,67]

Early management of systemic amyloidosis is crucial to avoid renal failure and death.[66] Control of underlying HS is foremost, as inflammation of the primary disease drives secondary amyloidosis. Successful treatment with the TNF-alpha inhibitor infliximab, resulting in marked improvement in both renal function and cutaneous manifestations of HS, has been reported in 2 cases.[68,70] In severe, refractory cases of HS that are unresponsive to medical therapy, surgical management of areas affected by HS may be considered in order to control inflammation and to stop progression of systemic amyloidosis.[67] Other medications, including azathioprine, methotrexate, cyclophosphamide, and chlorambucil, have been reported as treatments for systemic amyloidosis in other chronic inflammatory diseases, including rheumatoid arthritis and familial Mediterranean fever, but not for amyloidosis secondary to HS.[66]

Anemia

Anemia associated with HS has been attributed to 2 major etiologies: anemia of chronic inflammation and iron-deficiency anemia. Systemic inflammation due to HS may impair the body's ability to use iron and to absorb iron from the gut, resulting in low circulating serum iron levels despite adequate iron stores, and thereby causing anemia of chronic inflammation.[76] Iron deficiency anemia has also been observed in HS patients; while the cause is unclear, blood loss from HS wounds may contribute.[77] Finally, anemia may also be associated with systemic amyloidosis, which is itself a complication of HS.[66]

Although studies are limited, there seems to be a high prevalence of anemia in the HS population. Anemia has been associated with HS in 2 case series.[77,78] Further, a cross-sectional study from Denmark that included 462 HS subjects and 20,780 non-HS, control subjects, reported that 4.7% of HS patients had anemia.[76] Of 22 anemic HS subjects, 60% had a normocytic anemia, and 40% had a microcytic anemia.[76] Anemia in HS patients was generally observed to be mild; 3.72% of HS patients were found to have a mild anemia (6.5-7.5 mmol/L), while 0.23% had moderate anemia (5.0-6.5 mmol/L) and 0.70% had severe anemia (<5.0 mmol/L).[76] Notably, in this large study, anemia was not associated with HS after adjusting for age, sex, and smoking status, and after comparison with control subjects.[76] Therefore, despite the observed prevalence of anemia in HS patients, more studies are needed to establish whether anemia occurs as a consequence of HS.

Although anemia in HS tends to be mild,[76] severe anemia has been reported.[76,77] Notably, the severity of anemia does not seem to correlate with HS disease severity.[76] Symptoms of anemia include fatigue, headache, dizziness, shortness of breath, skin pallor, and tachycardia. Such clinical signs and symptoms in HS should prompt consideration of and workup for anemia.

Low hemoglobin and hematocrit levels confirm the diagnosis of anemia. Serum iron panel further differentiates anemia of chronic disease from iron-deficiency anemia, a distinction that is important in guiding management. Patients should be assessed for signs of ongoing blood loss. Persistent slow bleeding may occur from HS wounds.[77] HS patients with associated Crohn's disease or with peptic ulcers secondary to chronic NSAID use may have gastrointestinal bleeding. Appropriate workup should be undertaken to diagnose potential sources of bleeding.

Control of HS-associated inflammation is key to the management of anemia of chronic inflammation. Dietary modification and possibly iron supplementation may be indicated for management of iron-deficiency anemia. Management of possible gastrointestinal bleeding should be undertaken in conjunction with a primary care physician or gastrointestinal physician. Finally, severe or symptomatic anemia may require blood transfusion.[77]

Conclusion

Hidradenitis suppurativa is associated with a variety of cutaneous and systemic complications. These complications range from bothersome and distressing to potentially life-threatening. Development of complications can be avoided and minimized by controlling HS. In caring for HS patients, clinicians should be cognizant of the spectrum of potential complications and their associated signs and symptoms in order to practice early diagnosis and appropriate intervention.

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