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Anorectal disorders in the immunocompromised

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A B S T R A C T

Patients with anorectal complaints develop both typical and unusual anorectal pathology, and colorectal surgeons should be aware of the ways in which altered immunocompetence affects the diagnosis, treatment, and prognosis of benign and malignant anorectal disease. After reviewing what defines altered immunocompetence or the immunocompromised state, this article will review how this changes diagnosis, management, and in some cases, prognosis of anorectal disease.

Introduction

Anorectal complaints are common in immunocompromised patients.[1] A critical component of evaluating this patient population is determining what constitutes an immunocompromised state. A comprehensive history and physical with a particular focus on underlying diseases, environmental exposures, and any medications or immunosuppressive therapy is the first step. Some of these (eg, primary or congenital immunodeficiencies) are rarely encountered by colorectal surgeons. Others are evaluated more commonly, both in the inpatient and outpatient setting. These include human immunodeficiency virus (HIV) infection, malnutrition, diabetes mellitus, hematologic and solid organ malignancies (especially during hematopoietic stem-cell transplant or induction chemotherapy for leukemia), wound healing problems, and exposure to immunosuppressive therapies such as corticosteroids, cytotoxic chemotherapy, or biologic therapy for inflammatory bowel disease. Still others physiologically cause aberrations in immunity but are perhaps less clinically apparent or appreciated by surgeons: for example, renal or hepatic insufficiency, stress, allogeneic blood transfusion, and pregnancy.

Defining altered immunocompetence

When deciding whether a patient is immunocompromised, understanding underlying disease states and exposures can be augmented with laboratory studies. Low numbers of white blood cells such as CD4 + T helper cells or neutrophils can help in diagnosing and risk-stratifying patients. Neutropenia is defined as mild, moderate, and severe in most laboratories as an absolute neutrophil count (ANC) of 1000−1500 cells/μL, 500−1000 cells/μL, and less than 500 cells/μL, respectively.[2] Similarly, though developed for surveillance purposes and not to guide management, experts at the CDC have developed and updated HIV staging criteria that can assist with ascertaining disease control and degree of immunosuppression based on both CD4 counts (≥500, 200−499, and ≤200 cells/mL for mild, moderate, and severe) and clinical disease states, which include opportunistic infections, malignancies and any of a number of organ-specific pathology such as neuropathy or encephalitis.[3] In addition to clinical signs and symptoms, malnourished patients may have low serum levels of transferrin, prealbumin, or albumin.

Common anorectal problems and the immunocompromised

Hemorrhoidal disease and anal fissures

Hemorrhoidal disease is among the most common anorectal problems that a colorectal surgeon evaluates and treats. True incidence of this problem is difficult to ascertain given variations in definition. Widely cited epidemiologic work from the early 1990s using data from the United States and the United Kingdom estimated the prevalence at 4.4%.[4] It isn't clear from this data or from practice that immunocompromised patients are more prone to developing hemorrhoidal pathology. It is important to recognize however, as with any patient presenting with "hemorrhoids" that signs and symptoms are clearly elucidated, as it is common for the term to be used by patients as a catchall for anorectal complaints. Diagnosis is a clinical one and visualization of the anal canal with anoscopy and/or rigid or flexible proctosigmoidoscopy is important. Internal disease should be noted and graded, and any external disease should also be identified. Screening for colon and, in some cases, anal cancer should be completed as appropriate.

Management of hemorrhoidal disease in the immunocompromised, as in the immunocompetent, should start with conservative, non-operative options. These include dietary modification and stool bulking agents with adequate water intake. From there, other options,

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depending on disease, include a variety of topical therapies that generally consist of single or combination agents that reduce inflammation, swelling, anorectal spasm and pain: steroids, anesthetics, phlebotonics (eg, flavonoids), and astrigents (eg, witch hazel). Though they have a low risk profile and can address certain specific symptoms such as pruritus or bleeding, there is a lack of strong evidence that these agents will definitively treat the underlying disease.[5] More invasive interventions including rubber band ligation and hemorrhoidectomy, should be avoided in the immunocompromised. Wound healing can be a delayed, and in the case of the acquired immunodeficiency syndrome, may not occur at all, and the risk of infectious complications are high.[6,7] The only firm indications for surgical intervention in this patient population are incarcerated, gangrenous hemorrhoids or catastrophic bleeding. Injection sclerotherapy offers one option with lower risk in patients who have hemorrhoidal bleeding refractory to more conservative treatment.

Anal fissures are among the most common complaints of patients infected with HIV, along with condyloma and abscess/fistula.[8] At diagnosis, it is critical to fully evaluate the fissure with particular attention to ruling our malignant disease with biopsies, depending on its location (lateral or off-midline location is more atypical), appearance, and the duration of symptoms before proceeding with treatment. Moreover, immunocompromised patients can also develop rectal ulcerations that may be mistaken for anal fissures. In contrast to fissures, these lesions are more often related to lax sphincter tone, are characterized by a more "gnawing" persistent pain unrelated to bowel movements, are broad-based, invasive, and located more proximally than fissures.[9] Atypical fissures and ulcerations should be examined and biopsied for infectious etiologies such as syphilis, herpes, CMV, and neoplasia.

For more typical fissures, the initial approach to management is the same as in immunocompetent. Acute fissures (defined as duration <4–6 weeks) should be treated with a nonoperative approach: this includes increased fiber intake, optimizing bowel habits and stool bulk, warm tub soaks or Sitz baths which can help relax the internal anal sphincter, and topical agents such as calcium channel blockers or nitrates. This assumes that the etiology of the fissure is at least in part related to a hypertonic sphincter complex. Botulinum toxin is also an option that has a lower risk of long term incontinence when compared to lateral internal sphincterotomy but with a higher risk of recurrence.[10]

Anorectal infections

Human papilloma virus, condyloma acuminata and giant condyloma

Human papilloma virus (HPV) infection is exceedingly common in sexually active individuals. There are over 100 HPV subtypes, with both low risk and high risk strains, which can lead to high-grade dysplasia. The majority of patients infected with HPV are asymptomatic and clear the disease without treatment.[11] Other patients develop condyloma acuminata or anogenital warts, most commonly associated with HPV types 6 or 11.[12] Altered immunocompetence, particularly in HIV seropositive patients, affects the natural history of these infections and their clinical manifestations. Not only are these patients more likely to be infected and co-infected with high risk HPV subtypes, discussed later, but they can have a more virulent phenotype that is more resistant to treatment, has a higher rate of recurrence, and is more strongly associated with malignant transformation.[13] These risks exist similarly for transplant patients, with some authors noting that they should be screened for anal malignancy just as HIV positive patients are.[14] Immunosuppressed patients with condyloma should be treated similarly to those who are immunocompetent with the primary caveat being they should be closely surveilled for malignant degeneration and/or the development of premalignant/or malignant lesions. Furthermore, caution should be exercised in terms of excisional therapy in cases of extensive disease to avoid wound healing problems. A staged approach with close follow up might be prudent in such cases.

Though condyloma acuminata are benign lesions, there is a small but very real risk of malignant degeneration, particularly in immunocompromised patients. So called giant condyloma acuminata, also known as Buschke-Lowenstein tumors, is an intermediate grade lesion. Though they have both a benign-appearing histology and are not known to metastasize, they can invade surrounding structures in a "pushing" rather than infiltrative manner. Moreover, 50% of these can degenerate fully into a malignant lesion. These tumors are not subtle, presenting as large, exophytic masses with a cauliflower or polypoid appearance. They are rare, but occur most commonly in the setting of HIV seropositivity, post-transplant, hematologic malignancies, and prolonged steroid use.[13]

Perianal skin and soft tissue infections

Perianal skin and soft tissue infections are more common in immunocompromised populations than in the general population. Patients with hematologic diseases and malignancies are often admitted with neutropenia, which can both be a manifestation of the disease process (eg, myelodysplastic syndromes) or a consequence of immunosuppressive treatment regimens such as high intensity chemotherapy or bone marrow transplantation conditioning. Neutropenic-related infections including perianal infections and sepsis are among the largest sources of morbidity and mortality in this patient group. Based largely on single institutional series, the incidence of these infections, depending on the specific population, can range up to 9% with recurrence rates above 30% and mortality rates from systemic sepsis up to 60%.[7,15–17] In contrast to immunocompetent patients, these patients can present in a delayed fashion without clearly defined clinical signs of an infection beyond anal discomfort or pain and induration. Antibiotics are a first line treatment. Moreover, only a minority of patients will require incision and drainage, as the majority respond to systemic antibiotics, Sitz baths, and anal hygiene. Surgical drainage is reserved for patients who fail these measures, and notably, is fraught with chronic wounds and poor healing. For the colorectal surgeon asked to consult on the neutropenic or immunosuppressed patient with anal discomfort, it is critical that he/she remember the atypical presentation of perianal infection in this and high morbidity and mortality.[18]

Perianal premalignant and malignant disease

Anal intraepithelial neoplasia

Anal intraepithelial neoplasia (AIN) is a dysplastic, premalignant disorder affecting the squamous cells of the perianal area. It can be graded based on its histopathologic appearance into three grades: low (AIN I), moderate (AIN II), and high grade (AIN III). More recently, the grade of the disease has been simplified to low- or high-grade; other terms such as low or high grade squamous intraepithelial lesions (LSIL or HSIL), shared with the grading scheme for cervical dysplasia, are also used.[19] Similar to condyloma acuminata or genital warts (see above), AIN is a clinical manifestation of HPV infection with particular serovars. These so-called high risk serovars include types 16 and 18. It isn't clear why clinical disease such as condyloma or AIN varies across HPV subtypes and patient groups, but it is likely a result of the complex interplay between the virus and both the competent and incompetent immune system. A comprehensive review of the evaluation, diagnosis, and treatment of AIN is beyond the scope of this paper, but there are few important concepts relevant to the management of this disease in the immunosuppressed, which includes HIV infected patients, solid organ transplant recipients, and patients with autoimmune diseases.

First, though defining groups that might benefit from screening programs or close surveillance is difficult, immunosuppressed

individuals are among those that are at highest risk for developing anal neoplasia. Even in this group, screening is controversial given the problems with the currently available methodologies, primarily anal cytology, which has been reported to have high false positive rates in HIV infected patients.[19] At current, there are no formal guidelines regarding screening for anal cancer. The Infectious Diseases Society of America makes a weak recommendation for screening particular high risk groups HIV-infected men who have sex with men, women with a history of receptive anal intercourse or abnormal cervical Pap tests, and those with warts.[20] Both smaller observational studies and cohort studies have also demonstrated that solid organ transplant recipients have a fairly high prevalence of abnormal anal cytology and premalignant lesions (6–20%) with some groups arguing that these patients should also be screened.[21–23]

Second, it's important to recognize that HIV infection is associated with increased HPV infection risk as well as co-infection with high risk HPV serovars 16 and 18. This in conjunction with an impaired mucosal immune response and decreased ability to clear the virus have been postulated as reasons for the increased prevalence of AIN in HIV-infected patients. These patients are also at higher risk of progression from low to high grade AIN. Interestingly, in the era of antiretroviral therapy, though the prevalence of these premalignant lesions has remained unchanged, longer life expectancy may actually have increased the propensity of these lesions to progress to anal cancer. This is in contrast to the effect HIV therapy has on other HIV-associated malignancies such as Kaposi's sarcoma. Finally, the current United States Adult Immunization schedule recommends on a permissive basis (not included on routine vaccination schedules) HPV vaccinations in men aged 22–26 years old who have sex with men or are immunocompromised (eg, infected with HIV).[24]

Finally, when managing patients with AIN, it is critical to assess their immunocompetence. In general terms, the treatment of low grade AIN can either be expectant management with surveillance over some interval, typically 4–12 months, or any of a variety of topical or surgical treatments such as ablation (infrared coagulation, hyfrecation, argon plasma coagulation, radiofrequency ablation) or excision. Patients who are immunosuppressed may warrant closer surveillance (3–6 months). These patients tend to have recurrent, resistant, and multifocal disease.[25] Because of this, ablative therapies should probably be limited where possible, and a combination of close surveillance and topical therapies used, with ablation reserved for more sinister appearing lesions.

Anal squamous cell cancer

Anal cancer – specifically, squamous cell carcinoma of the anal canal and perianal skin – is an uncommon malignancy, with just over 8000 cases annually. Among the risk factors for developing these malignancies are high risk HPV virus infection (most frequently HPV 16) and the immunosuppressed state such as the HIV infected, solid organ transplant recipients, and those with autoimmune diseases requiring medical therapy.[26–28] The diagnosis and work-up is essentially unchanged from that of immunocompetent patients and will not be reviewed in this article. When it comes to differences in the approach to the immunosuppressed population, there are considerations for anal neoplasia screening, as discussed above. Furthermore, there is the question of whether immunosuppressed patients with localized disease have similar outcomes with the preferred definitive treatment of chemoradiotherapy. By and large, most HIV positive patients are going to be treated similarly to those without HIV infection; in immunocompetent patients, disease response rates are excellent with 5-year overall survival above 70%.[29,30] Outcomes in HIV patients have several important differences with implications for surveillance and patient education. Prior to the advent of antiretroviral therapy, small observational studies noted worse outcomes with higher rates of recurrence and poorer treatment tolerance.[31,32] These studies and more recent, larger studies in the era of antiretroviral therapy have suggested that survival differences are small (HIV-positive 77% v. HIV-negative 75% at 2 years).[33–35] That said, a recent systematic review that pooled results from eight comparative, uncontrolled studies, most of them in the antiretroviral era, showed a 3-year mortality relative risk of 1.77 (95%CI, 1.35–2.32). Overall 5-year survival appears to have a wider range in the HIV-positive population (20–88% v. 65–84%). Critical to the interpretation of this is that many of these deaths were not cancer specific. Pooled rates of disease-free survival (again, non-comparative) at three years were similar (75%) to those in HIV negative patients. Concerns regarding increased grade 3/4 toxicities (specifically cutaneous toxicities) and long-term local control of disease remain, even though the patients in these studies are characteristically young with good performance status and CD4 counts above 200 U/L.[33] Local relapse and recurrence in the HIV-positive population are up four times higher at three years even in patients on antiretroviral therapy. The reasons for this are multifactorial – toxicities resulting in dose reductions and treatment interruptions; heterogeneity in terms of toxicity reporting; and the interactions of therapy such as protease inhibitors or prophylactic antibiotics with chemotherapy and radiation.

There are several areas of investigation and approaches to improving control of disease after definitive chemoradiotherapy in HIV-positive patients. These include topical or systemic maintenance therapy (cyclooxygenase-2 inhibitors, epidermal growth factor receptor antagonists, immunotherapy), human papillomavirus vaccination, and chemoprevention.[36] Data to date is lacking for these interventions.

Conclusion

Immunosuppressed patients with anorectal pathology require special attention to their, at times, atypical presentations, overall increased risk profile for anorectal infections, premalignant, and malignant diseases, and how their state changes management. In general, assessing the degree of the immunosuppression before embarking on a treatment plan is critical. These patients may benefit from screening, and regardless of treatment, should be closely surveilled, judiciously intervened on, particularly in the operating room, and thoroughly educated on how their oncologic outcomes differ from the immunocompetent.

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