Tumors of the Anal Canal

Marco Ettore Allaix, MD, Nora Eve Joseph, MD, and Alessandro Fichera, MD, FACS, FASCRS

GENERAL CONSIDERATIONS

The surgical anal canal extends from the level of the pelvic floor (the anorectal ring or the junction of the puborectalis portion of the levator ani muscle with the external anal sphincter) to the proximal margin of the anal verge. Thus defined, the anal canal corresponds to the extent of the sphincter complex and is approximately 4.0 cm in length. At midpoint is the dentate line, which is defined macroscopically by the anal valves and bases of the anal columns. Microscopically, the anal canal is divided into three zones based on characteristic histologic features. The upper zone lies proximal to the dentate line and is lined by colorectal type glandular mucosa. Extending distally from the dentate line is the mid or anal transition zone (ATZ) defined by a specialized or transitional type epithelium. The third and most distal zone is comprised mostly of non-keratinized and occasionally keratinized squamous mucosa (Figure 1).

The ATZ has been intensively studied for its role in continence and as a potential site for neoplastic degeneration after stapled ileoanal anastomosis in patients with ulcerative colitis. In the literature, this epithelium has been variously classified as transitional, intermediate, or cloacogenic. The ATZ epithelium may also contain mucin-producing cells, endocrine cells, and melanocytes.

The arterial blood supply of the anal canal derives from the superior, middle, and inferior rectal arteries, whose terminal branches reach the anal submucosa. Three main arterial trunks in the right anterior, right posterior, and left lateral positions can be isolated below the dentate line. They originate primarily from the superior rectal artery. The middle rectal veins drain the upper anal canal into the systemic system via the internal iliac veins. The inferior rectal veins drain the lower anal canal, communicating with the pudendal veins and draining into the internal iliac veins.

Lymphatic drainage of the anal canal varies based on the level: below the dentate line drainage is to the inguinal lymph nodes; above, lymphatic drainage goes to the mesorectal, lateral pelvic, and inferior mesenteric nodes.

With focus primarily on anal neoplasms, presenting symptoms are often nonspecific and may include pain, bleeding, discharge, pruritus, and ulceration. Frequently, anal tumors are completely asymptomatic and are diagnosed only incidentally, or because of palpable inguinal lymph nodes.

The macroscopic appearance of an anal lesion may be nonspecific also: it may be flat or raised, and the surface may be verrucous, erythematous, or scaly. An ulcerated mass is usually very suspicious of malignant degeneration.

Diagnosis of anal neoplasm requires a high index of suspicion, particularly in patients with known risk factors who present with new symptoms. For a definitive diagnosis, a biopsy of the suspicious area is often indicated, unless the patient has severe immunocompromise.

Imaging is used for cancer staging. Magnetic resonance imaging of the pelvis and endoanal ultrasound scan define tumor size and invasion and the involvement of local lymph nodes. Distant metastatic spread can be assessed with computed tomographic scan of the chest, abdomen, and pelvis.

The various elements of the anal canal account for the different neoplasms that are described: (1) squamous cell tumors, including condyloma acuminatum, flat squamous dysplasia, Bowen's disease, and invasive squamous cell carcinoma and its variants; (2) adenocarcinoma and its variants, including rectal-type adenocarcinoma, the so-called anal gland adenocarcinoma, fistula-related mucinous adenocarcinoma, and intraepithelial adenocarcinoma (i.e., Paget's disease); (3) neuroendocrine neoplasms, including carcinoid tumor, small cell carcinoma, and non–small cell high-grade neuroendocrine carcinoma; (4) malignant melanoma; (5) mesenchymal tumors; and (6) malignant lymphoma. Although these anal canal tumors as a group account for only about 1.5% of all gastrointestinal neoplasms, their diagnosis and management can be challenging for pathologists and clinicians alike.

SQUAMOUS NEOPLASMS

Condyloma Acuminatum (Anal Wart)

Condyloma acuminatum, or anal wart, is caused by human papilloma virus (HPV). HPV is the most common sexually transmitted infection. Its incidence rate has increased over the past 30 years. In the United States, the prevalence rate of anogenital HPV is estimated to be 15%, equal to 24 million individuals. In addition, 500,000 to 1 million new cases of genital warts are believed to occur annually, resulting in 600,000 healthcare provider visits per year. Currently, more than 100 different HPV types have been sequenced and officially classified, about one third of which have been found to infect the anogenital epithelium.

Although the natural history and the potential for progression to squamous dysplasia and squamous cell carcinoma still needs to be completely elucidated, condyloma acuminatum (anal wart) is generally regarded as a premalignant lesion. The incidence rate of squamous cell carcinoma of the anus in patients with anal condyloma has been reported to be up to 4%. The key histologic features of condyloma acuminatum are a verrucous architecture composed of papillary excrescences and hyperkeratosis as well as the presence of koilocytic changes within a maturing squamous epithelium. Koilocytes are epithelial cells displaying characteristic changes secondary to HPV infection: vacuolated cytoplasm, wrinkled, hyperchromatic nuclei and perinuclear halos. Binucleated and trinucleated epithelial cells are also often present (Figure 2). Koilocytic changes may be absent, however, when the viral infection subsides.

Although many anal condylomata, particularly those of perianal skin, are caused by low-risk HPV (types 6 or 11) and should therefore be regarded as low risk for progression, those lesions in the anal canal are often associated with high-risk HPV (such as 16) and are more likely to progress to an invasive cancer. This is particularly true in patients with immunocompromise.

Several different medical and surgical approaches have been proposed for the treatment of anal condylomata with limited clinical data to support. No consensus has been reached on a gold standard, and whether treatment eliminates infectivity is not even clear, given the fact that both topical and surgical treatments are only aimed at eradication of the visible lesions. Topical treatments include podophyllotoxin, imiquimod cream, and trichloroacetic acid. Invasive therapies include cryotherapy, argon plasma beam treatment, and surgical excision/fulguration. Repeated sessions are needed with cryotherapy that is mainly indicated for small lesions. Surgical excision/fulguration and argon plasma beam treatment are highly effective in the short term. It is mandatory to submit several samples to the pathologists for definitive diagnosis of these lesions that may harbor an invasive component. Skin bridges must be left intact

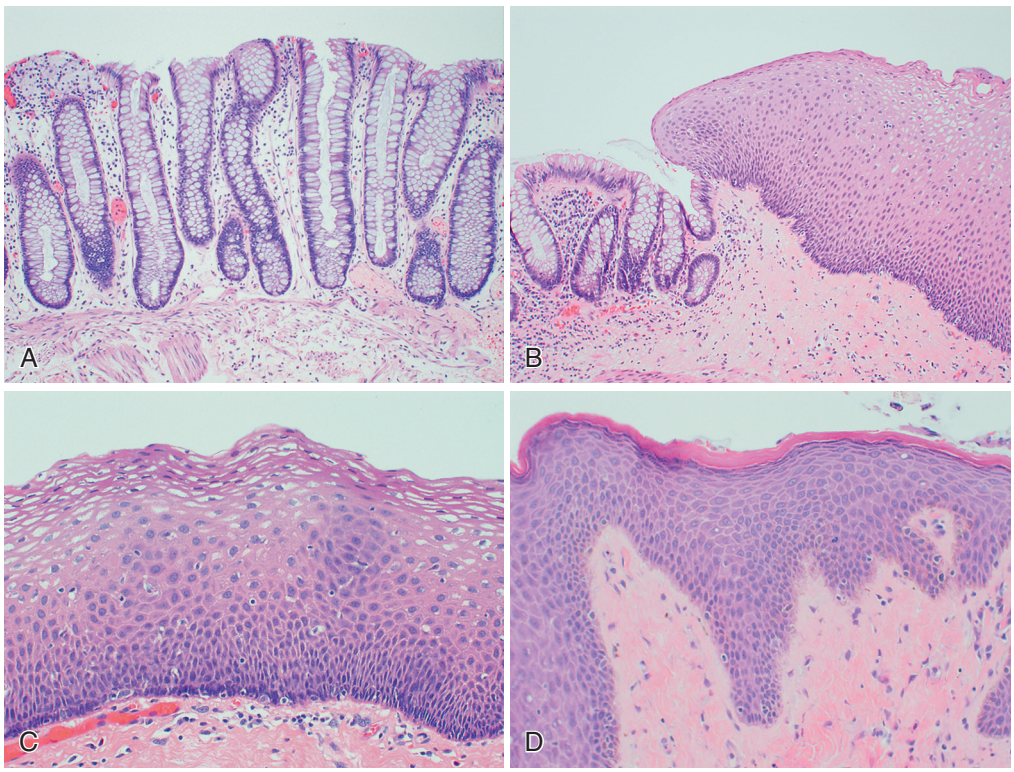

FIGURE 1 **A,** Normal columnar epithelium lining the upper zone of the anal canal. **B,** Normal mid zone transition from proximal to distal *(left to right)*. **C,** Normal non-keratinized and **D,** keratinized stratified squamous epithelium of the distal anal canal.

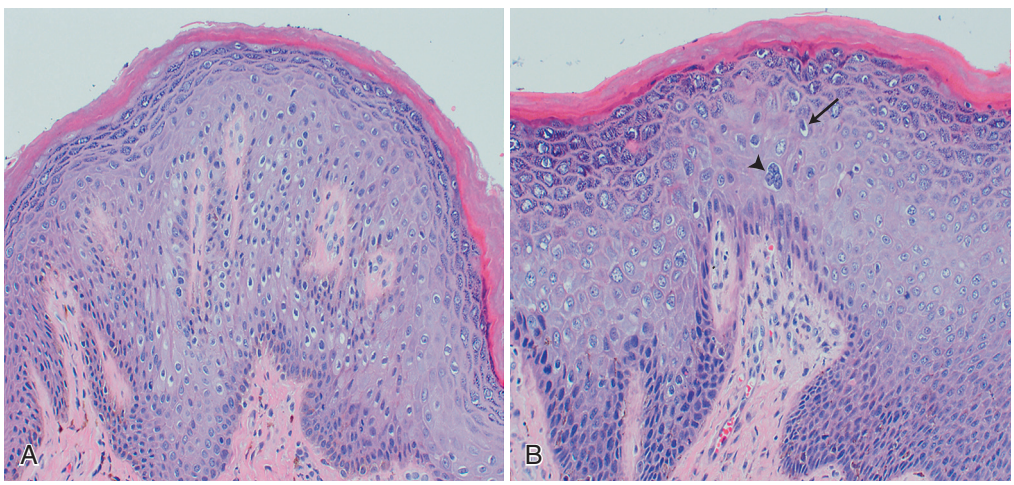

FIGURE 2 **A** and **B,** Condyloma acuminatum. Papillae of squamous mucosa with features of HPV infection: hyperkeratosis, koilocytic change *(arrow)* and trinucleation *(arrowhead)*.

between wounds to minimize scarring and to avoid anal stenosis (Figure 3).

The many topical treatments have very limited efficacy in the presence of large lesions and are associated with significant side effects. They should be considered only in addition to surgical eradications or in patients with compromised conditions that would not tolerate surgery. Podophyllin has potential oncogenic and teratogenic effects and should not be applied on the cervix and in the anal canal or used during pregnancy. Marrow suppression, hepatic dysfunction, neurologic effects, hallucinations, psychosis, nausea, vomiting, diarrhea, abdominal pain, and genital burns have been rarely described. Trichloroacetic acid may cause an intense burning sensation and ulceration to the dermis and is therefore not recommended for large warts. 5-Fluorouracil has limited use because of its severe local effect and teratogenicity. Conflicting results have been reported with interferon, which is an expensive drug with significant systemic side effects. Imiquimod is not recommended during pregnancy or for internal use. Mild to severe erythema may occur; other side effects include localized erosions, an impetigo-like reaction, and an itching or burning sensation.

Overall recurrence rates between 20% and 50% have been reported irrespective of the treatment approach. Still unclear is whether disease recurrence is the result of recrudescence, reinfection, or other factors such as individual immune response or inadequate treatment. The presence of genital HPV types in plucked pubic and perianal hair suggests that an endogenous reservoir for HPV may play a role in recurrence. Thus, if only the visible lesions are destroyed, latent HPV likely remains in the surrounding tissue. The lack of antiviral activity of most recommended topical therapies supports this hypothesis.

The immune system appears to play a major role in regression of genital HPV disease. In patients with spontaneous regression, significant differences are present in the epidermal and dermal concentration of CD4+ activated memory lymphocytes compared with those without regression. Although there is an association of serum antibodies to HPV proteins with HPV-related diseases, their role is uncertain because their presence does not correlate with wart regression. Evidence suggests that T cells in male and the female genital epithelium secrete protective antibodies against many HPV infections, but the significance of this is unclear. Anal condylomata in patients with immunosuppressed conditions treated with surgery has a higher recurrence rate and recurrence at a faster pace than in patients with a competent immune system. In patients with human immunodeficiency virus (HIV)-seropositive conditions, CD4 counts should be maximized to prevent early recurrence.

Many pharmacologic topical treatments have been proposed to reduce recurrence after surgical treatment. Imiquimod and interferon are the only drugs that exhibit antiviral activity. Both have shown lower recurrence rates compared with other therapies. In particular, adjuvant interferon treatment can reduce recurrence after surgical excision and is more effective in patients with condylomata present for more than 6 months and in the presence of HPV subtype 6 or 11. Further evidence shows that, particularly in patients with immunocompromise, immunostimulation may lead to a reduction in the size of lesions and in recurrence after surgery.

First described by Buschke in 1886, and later by Buschke and Lowenstein in 1925, the "giant condyloma of Buschke and Lowenstein" (or verrucous carcinoma) is a rare form of condyloma that refers to a slow-growing neoplasm that has a tendency to recur and to form abscesses and fistulae. It is an intermediate form between condyloma acuminatum and squamous cell carcinoma. This tumor does not appear to arise from malignant transformation of a condyloma but represents a low-grade form of squamous cell carcinoma. Like conventional condylomata, these lesions are more likely to be associated with low-risk HPV. The histologic appearance on a biopsy specimen may be identical to that seen in common condyloma acuminatum (surface hyperkeratosis, prominent acanthosis and papillomatosis, with orderly arrangement of the epithelial layers). However, excision specimens often demonstrate an endophytic component that is not present in ordinary condylomata. The biology of such lesions is typically that of local invasion without metastasis. The treatment consists of complete wide local excision often requiring

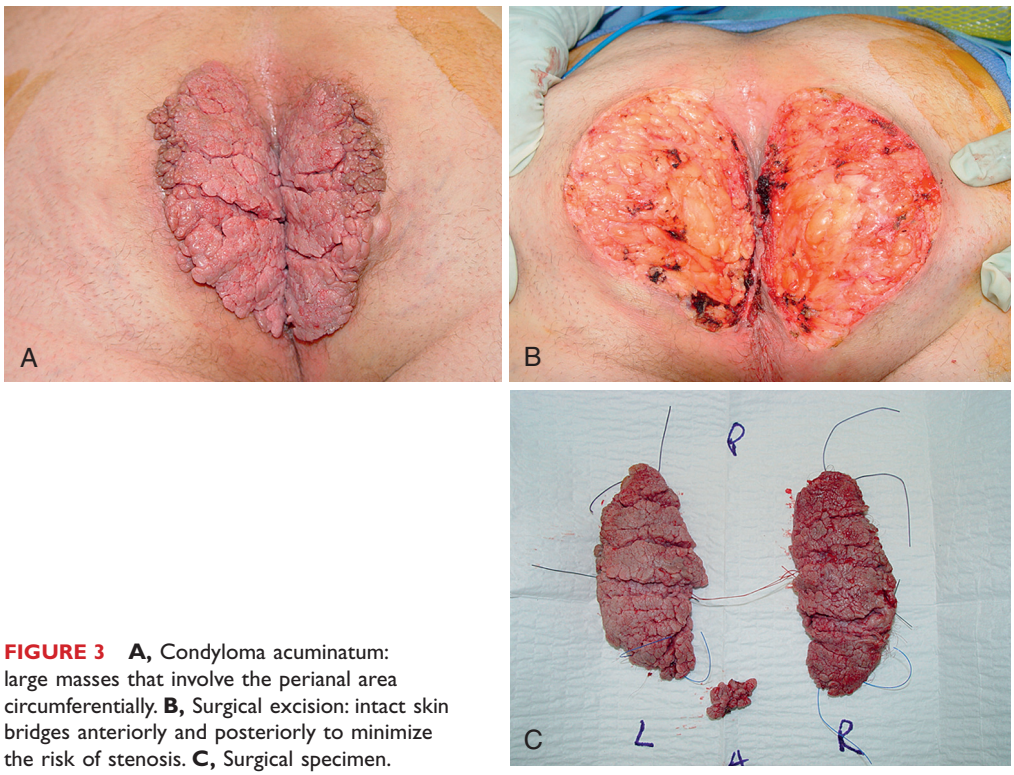

FIGURE 3 **A,** Condyloma acuminatum: large masses that involve the perianal area circumferentially. **B,** Surgical excision: intact skin bridges anteriorly and posteriorly to minimize the risk of stenosis. **C,** Surgical specimen.

flap closure. An abdominoperineal resection is required in case of deep tissue involvement (Figure 4). The role of chemoradiotherapy is still unclear and seldom indicated.

Anal Intraepithelial Neoplasia

Anal intraepithelial neoplasia (AIN) is often a precursor to invasive squamous anal carcinoma. The disease process may involve both the perianal skin and the anal canal, including the anal transition zone, but anal canal lesions without evidence of perianal involvement are very unusual. It is a multifocal disease process strongly associated with human papillomavirus (usually HPV types 6, 11, 16, and 18). Strong etiologic and clinical similarities are seen between AIN and cervical (CIN) and vulvar (VIN) intraepithelial neoplasia.

AIN is characterized by cellular and nuclear abnormalities within squamous epithelial cells limited to the basement membrane. Histologic features include nuclear atypia such as pleomorphism, enlargement and hyperchromasia as well as increased mitotic activity above an expanded basal layer. The extent of basal layer expansion, or loss of maturing epithelium, is the basis for grading dysplasia in tissue biopsies of anal lesions. AIN I refers to nuclear abnormalities confined to the lower one third of the epithelium and is considered a low-grade dysplastic lesion. AIN II and III are high grade lesions with AIN II limited to the lower two thirds and AIN III involving the full-thickness of the epithelium, or carcinoma in situ (Figure 5). In anal cytology the Bethesda grading system categories dysplastic lesions as low-grade squamous intraepithelial lesions (LSIL) and high-grade intraepithelial lesions (HSIL). LSIL is equivalent to AIN I seen in a tissue biopsy and HSIL encompasses AIN II and III.

The exact prevalence rate of AIN in the general population is unknown, but it is thought to be less than 1%. Identified risk factors for AIN include HPV infection, anal warts, multiple sexual partners, men who have sex with men, anal receptive intercourse, cervical dysplasia or cancer, smoking, and immunosuppression (such as in transplant and HIV).

Although AIN I and II have been known to have the potential to regress, AIN III very rarely regresses. The risk of progression of AIN to invasive anal cancer approximates 10% at 5 years in patients with immunocompetent conditions and up to 50% in patients with immunosuppressed conditions. Those at the highest risk of invasive cancer are those with multifocal disease or immunocompromise.

A high index of suspicion is required for diagnosis of AIN. Around 10% of AIN lesions are diagnosed as an incidental finding after excision of an "innocent" anal tag or condyloma-like lesion. AIN III lesions are usually flat, and their appearance is variable. The presence of ulceration in an AIN lesion suggests invasion. Symptoms include pruritus and anal discharge; other symptoms of pain, bleeding, and tenesmus suggest invasion.

No consensus exists about the best management of AIN. The primary goal is to prevent the development of anal cancer and minimize symptoms. Proposed strategies range from watchful waiting to aggressive surgery.

Conservative strategies are supported by the high recurrence rates seen after aggressive attempts at complete eradication. This is particularly true in patients with HIV and is likely the result of persistent HPV infection. Also, the rate of progression of high-grade AIN to invasive cancer is relatively low with the possibility of detection of invasive disease at an early and still treatable stage.

Ablative therapies used in AIN include CO_2 laser ablation, cryotherapy, and electrocautery fulguration. All the options are burdened by high recurrence rates and significant morbidity.

Excision of small lesions for histologic evaluation is preferred to purely ablative therapy because the latter precludes the possibility of a definitive diagnosis to guide further management. In the authors' practice, for definition of the extent of disease at diagnosis, anal mapping and anal pap smear with excision/ablation of the suspicious areas is performed. This should be done with high-resolution anoscopy (HRA). The advantage of HRA is more accurate identification of the suspicious lesions and minimization of damage to surrounding healthy tissue. In brief, this technique is based on the principle that, with the application of acetic acid, dysplastic tissue exhibits

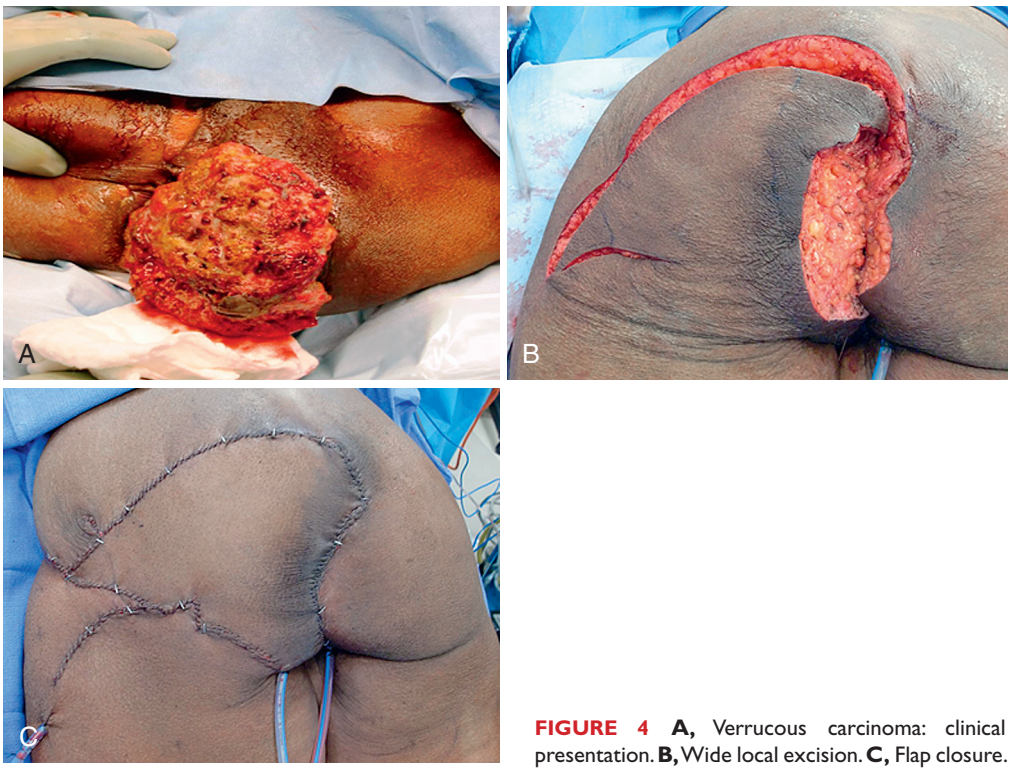

FIGURE 4 **A,** Verrucous carcinoma: clinical presentation. **B,** Wide local excision. **C,** Flap closure.

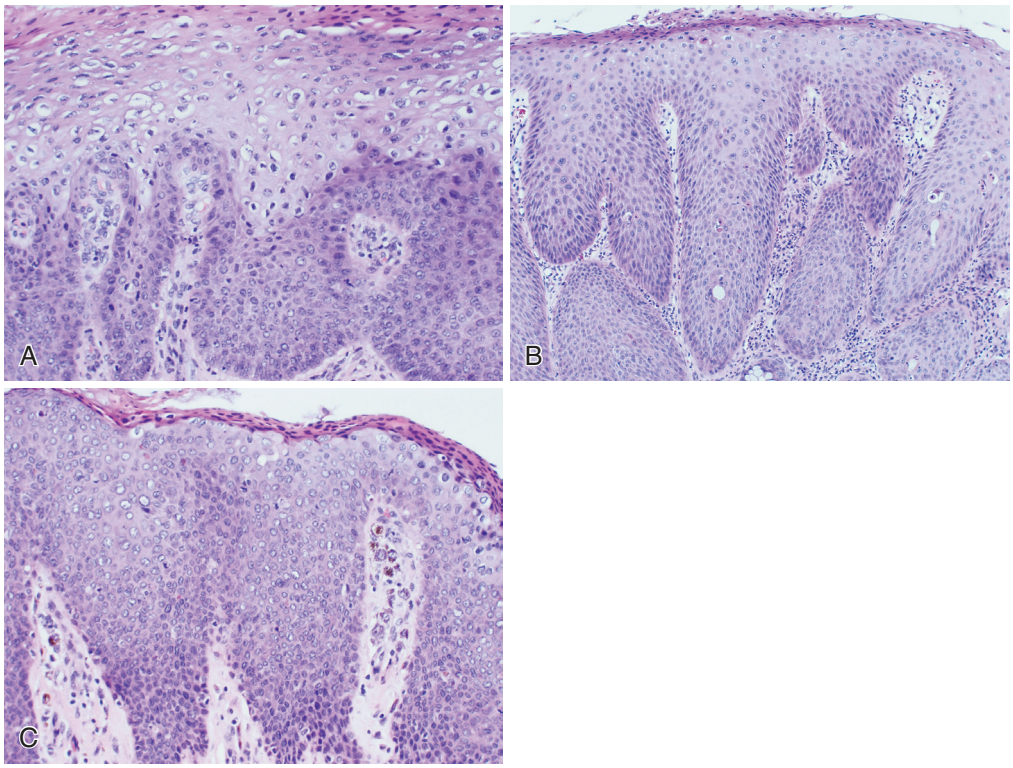

FIGURE 5 **A,** Human papilloma virus (HPV) infected epithelial cells can become dysplastic. The earliest form of dysplasia, or anal intraepithelial neoplasia I (AIN I), is limited to the lower one third of the epithelium. **B,** In AIN II, the grade of dysplasia increases as evidenced by expansion of cellular abnormalities and increased mitotic activity into the lower two thirds of the epithelium. **C,** Dysplastic cells take over the entire epithelium in AIN III, the highest grade of dysplasia. Note the complete loss of an identifiable basal layer with the top of the epithelium identical in appearance to the bottom. Further progression leads to invasive squamous cell carcinoma.

distinct changes and patterns in the anal mucosa. After application of 5% acetic acid to the anal canal and perianal skin, tissues that harbor AIN turn acetowhite. Acetowhitening alone is nonspecific. It sets the background on which the clinicians identify the characteristic vascular changes of low-grade and high-grade dysplastic lesions. Lugol's solution may be applied in areas of diagnostic uncertainty. Areas that do not take up Lugol's solution are considered at high risk for harboring high-grade dysplastic tissue. A biopsy of these areas should be obtained.

After the initial diagnosis is reached and invasive cancer has been ruled out, the authors continue to follow the patients with anal pap smear, excision of the suspicious areas, and fulguration of the less concerning lesions.

Other treatments, such as photodynamic therapy, immunomodulation therapies with imiquimod cream and cidofovir gel, and HPV immunotherapy, have been proposed. Although they are promising, the data are too limited to draw any definitive conclusions regarding their long-term efficacy.

Bowen's Disease

Bowen's disease is synonymous with AIN III. Patients with anal-margin Bowen's disease typically present with minor symptoms, such as burning or pruritus. Up to a third of the patients report a mass or bleeding. Clinically, Bowen's disease presents as erythematous, occasionally brown-red pigmented, noninfiltrating, scaly, or crusted plaques, that sometimes have a moist surface or even nodules (Figure 6). Differential diagnosis is extensive and includes different benign dermatologic conditions like psoriasis, eczema, and leukoplakia. The standard treatment is wide surgical excision. To ensure clear resection margins, a systematic four-quadrant biopsy technique, with intraoperative frozen sections including intraanal biopsies, has been advocated. Despite a wide excision, recurrence rates up to 30% have been reported. The major disadvantage of wide local excision is the difficulty to primarily close the wound; skin flaps may be necessary. Given the multifocality of these lesions, anal mapping is often performed in the authors' practice. Four-quadrant biopsies are obtained, starting at the dentate line, at the anal verge, and on the perianal skin (Figure 7). They are sent separately to the pathologist for permanent section.

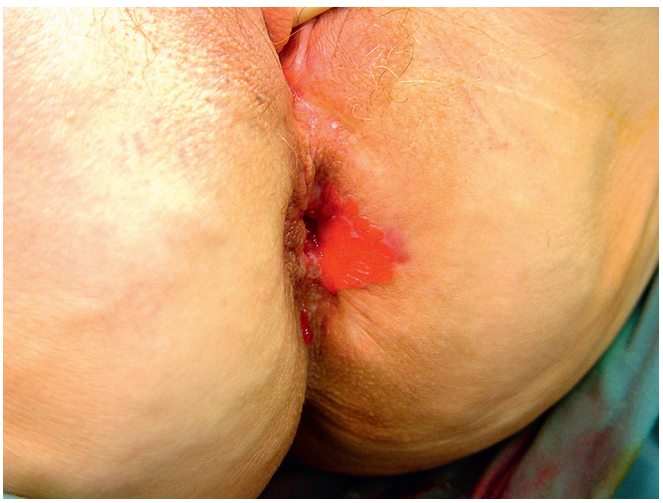

FIGURE 6 Bowen's disease: clinical presentation as brown-red pigmented, noninfiltrating, scaly plaques, with a moist surface and nodules.

Squamous Cell Carcinoma

Traditionally squamous cell carcinoma of the anal canal occurs more frequently in women than in men (1.5 vs 1.0/100,000). Epidemiologic studies have shown that most anal cancers are associated with HPV infection, predominately oncogenic types 16 and 18. Anal intercourse is among the presumed mechanisms by which HPV is introduced into the anal canal. Other risk factors include

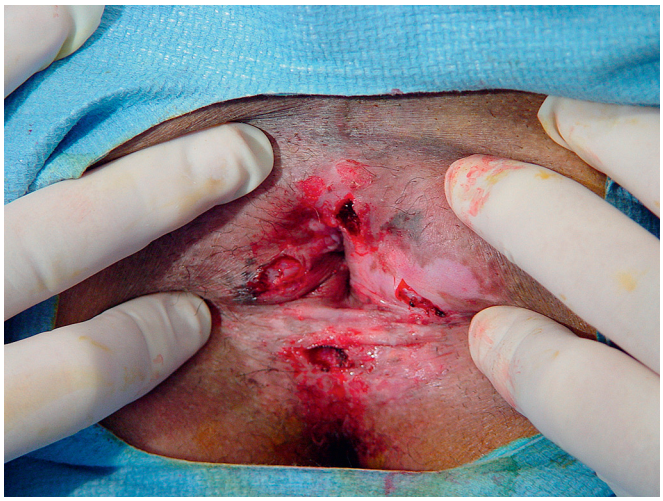

FIGURE 7 Anal mapping for Bowen's disease. Four-quadrant biopsies are obtained, starting at the dentate line, at the anal verge, and on the perianal skin. They are sent separately to the pathologist for permanent section.

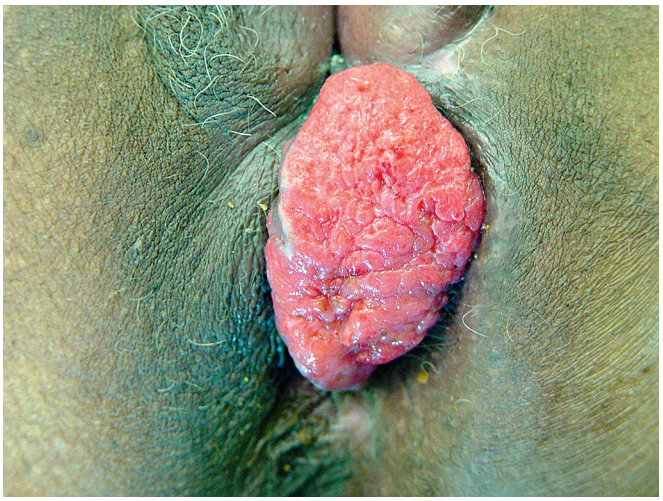

FIGURE 8 Anal squamous cell carcinoma: fungating mass at the anal verge.

immunosuppression (transplant, immune disorders, and HIV infection), an increasing number of sexual partners, a history of anogenital warts, previous lower genital tract dysplasia or carcinoma, and a history of smoking.

The clinical presentation is nonspecific (Figure 8). Anal bleeding appears to be the most common presenting symptom. Squamous cell carcinomas (SCC) are defined histologically by invasion of tumor cells beyond the basement membrane. Upon resection each tumor is given a grade and pathologic stage according to the TMN staging system (Figure 9). Although previous editions of the WHO classified three subtypes of SCC's current guidelines recommend a generic line diagnosis of "squamous cell carcinoma" due to low reproducibility and lack of prognostic relevance. However, the WHO does suggest adding a comment regarding the presence of additional histologic features such as degree of keratinization, cell size, basaloid features and adjacent AIN.

Before 1974, the management of squamous cell carcinoma of the anal canal consisted of primary surgical treatment in the form of an abdominoperineal resection. Since then, Dr Norman Nigro introduced his regimen. In his original description in three patients, radiation was given as a 3000-rad full-pelvis dose calculated to the mid plane of the pelvis, delivered in 15 treatments of 200 rad each in a 3-week period. The day after the start of radiation therapy, patients were given 25 mg/kg body weight of 5-fluorouracil daily continuous infusion for 5 days. Also, on the first day, the patients were given mitomycin-C, 0.5 mg/kg body weight. This protocol has undergone several modifications over the years, but it has completely revolutionized the treatment of squamous cell carcinoma of the anal canal, turning it into a "medical disease," with surgery indicated only as salvage therapy for persistent or recurrent disease. Combined modality therapy is delivered to the primary tumor and the locoregional lymph nodes, achieving complete response and 5-year overall survival rates as high as 92%. The presence of inguinal lymph node metastases at diagnosis reduces 5-year overall survival rates to 58%. Approximately, 10% to 15% of patients eventually have distant metastases develop, most commonly in the liver and lungs, and lymph node metastases occur in 10% to 25% of cases.

Controversy persists about the approach to the inguinal lymph nodes. Some authors favor prophylactic inguinal irradiation, and others reserve inguinal irradiation only for patients with histologically proven inguinal metastases. Inguinal irradiation has a 48% rate of acute and late morbidity. Moreover, in series of patients treated with the "Nigro protocol" avoiding the inguinal fields, inguinal

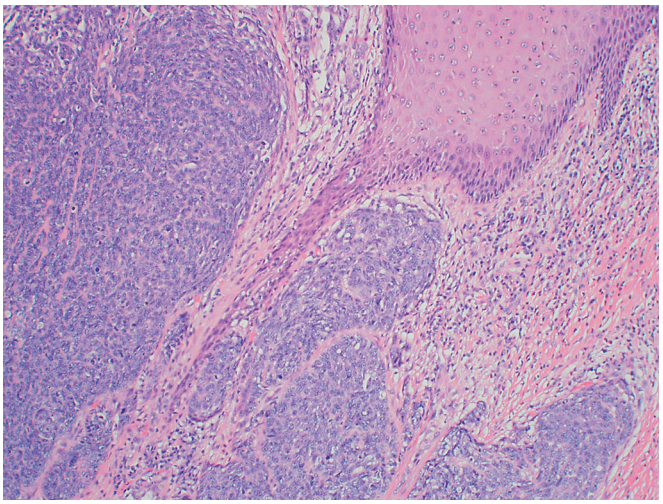

FIGURE 9 Although some residual nonneoplastic epithelium is present in the upper right hand corner, the majority of cells are malignant squamous cells invading through the lamina propria and submucosa (not identified in this image).

metastases were observed in 7% to 8% of patients, with the hypothetical potential risk of overtreating 92% to 93% of patients. Irrespective of the treatment the patient has undergone, surveillance of the inguinal lymphonodal stations remains critically important to detection of early inguinal metastases. Because lymph node size at the imaging studies is not a reliable predictor of metastases, the use of sentinel lymph node biopsy has improved staging of the inguinal status in these patients and is considered the procedure of choice for correct staging.

Inguinal lymph node dissection is associated with high morbidity: an overall wound infection rate of 24%, an incidence rate of moderate to severe infection of 16%, and lower extremity edema in 40% of patients. Superficial groin dissection involves only the inguinal nodes, and a deep groin dissection includes also the iliac and obturator nodes. Through a diagonally oriented skin incision from a point medial to the anterior superior iliac spine down to the apex of the femoral triangle, the fat and lymph nodes are dissected from the

femoral triangle, starting medially at the lateral edge of the adductor longus and proceeding laterally. The femoral vessels are preserved, and the saphenous vein is ligated and divided. Finally, the lymph nodes are dissected free from the femoral nerve. The deep groin dissection begins with the division of the inguinal ligament. The deep circumflex iliac vessels are ligated, and the peritoneum is separated from the preperitoneal fat and nodes by means of blunt dissection. Then, the chain of lymph nodes along the external iliac vessels is dissected until the origin of the internal iliac vessels. The dissection incorporates the nodes overlying the obturator foramen. After the lymph nodes have been removed, the inguinal canal is reconstructed to prevent hernias.

Although in the era of improved antiviral therapy, the disease-related outcomes are similar (5-year overall survival rate about 71% to 75%), tolerability of combined modality therapy seems to be worse in patients with HIV-positive conditions in the setting of low CD4 T-cell counts. The "Nigro protocol" has been proven to be very effective, but a small percentage of patients still do not respond to it and an equally small percentage eventually have local recurrence. Interestingly, patients that do not respond have a worse outcome after salvage surgery, typically an abdominoperineal resection, even when an R0 resection is achieved. The 5-year overall survival rate after salvage surgery for persistent disease is 31% to 33%, compared with 51% to 82% after surgery for local recurrence. This is likely the result of more aggressive tumor biology. When to declare a patient a non-responder is another topic of controversy. The radiation oncology literature clearly shows that the effects of treatment may continue for several months. In the authors' practice, a biopsy is not performed for 6 months to a year after the end of treatment.

Options for patients with metastatic anal cancer are limited and primarily involve combination chemotherapy. A regimen consisting of 5-fluorouracil and cisplatin has been the most frequently studied and results in overall response rates of around 60%, most of which are partial responses. The median survival time is approximately 12 months.

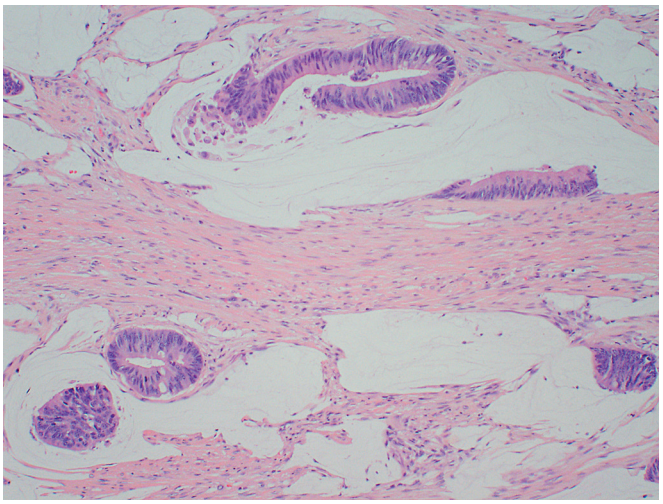

FIGURE 10 Invasive mucinous adenocarcinoma. Note the malignant glands arising from columnar epithelium floating in mucin pools.

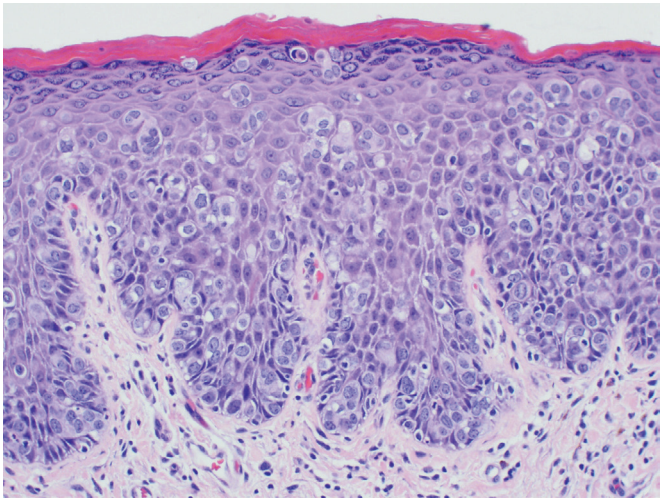

FIGURE 11 Extramammary Paget's disease. Many individual, large, pale cells represent adenocarcinoma in normal external squamous mucosa of the anal skin.

ADENOCARCINOMA

Adenocarcinoma of the anal canal accounts for about 10% of all anal canal cancers. Most of these neoplasms show a colorectal phenotype and originate from the columnar epithelium in the upper portion of the anal canal or from the glandular cells of the ATZ zone (Figure 10). Adenocarcinoma can also arise from anal glands and within established fistulas. The WHO categorizes these entities as extramucosal (perianal) adenocarcinomas.

Although the distinction between these tumors and the truly lower rectal adenocarcinomas directly extending into the anal canal is often very difficult, the difference is purely semantic because the treatment algorithm is the same. For stage II and III lesions, the treatment consists of neoadjuvant 5-fluorouracil–based combined modality therapy, then surgery often as an abdominoperineal resection, finally followed by 5-fluorouracil–based consolidation chemotherapy. For stage I, surgery alone is sufficient, and as in rectal cancer, for small very superficial T1 lesions with favorable histologic features, the role of local excision is currently debated.

Paget's Disease

Perianal Paget's disease is a rare clinical entity with only a few hundred cases reported in the literature. In its early stages symptoms are often limited, therefore, diagnosis and treatment is usually delayed. In addition, the condition can be confused with eczema or dermatitis, thus further delaying treatment. In many patients, the disease is present several years without progressing. Histologically, pale tumor cells with abundant clear cytoplasm and large nuclei are seen infiltrating throughout non neoplastic squamous epithelium (Figure 11). There are two proposed etiologies. The first is a true primary lesion of apocrine glands exhibiting epidermotropism. These lesions are seen primarily in white women over the age of 50, have a high local recurrence rate and often express markers of apocrine cells. The other lesions are considered synchronous or metachoronous lesions in patients with internal malignancies (33% to 86% have colorectal adenocarcinoma, or carcinomas of the Bartholin glands, urethra, bladder, vagina, cervix, endometrium, or prostate).

Staging classification of perianal Paget's disease and stage-appropriate treatment protocols have been proposed. Prognosis remains good for stage I (Paget's cells found in perianal epidermis and adnexa without primary carcinoma), but it progressively worsens for stage II (invasive cutaneous disease penetrating the basement membrane into the underlying stroma or synchronous localized malignancies: i.e., IIa adnexal malignancy, IIb visceral malignancy) and for stages III and IV, where regional involvement and distant metastatic disease are present, respectively.

The treatment of Paget's disease is surgical. However, because Paget's disease typically extends microscopically beyond the visible

lesion, it is difficult to obtain a negative margin without sacrificing large skin areas. Consequently, recurrence rates between 30% and 70% after surgery have been reported.

Nonsurgical approaches have been advocated in selected cases, for those patients who are medically unfit for surgery or wish to avoid radical surgery or those who have multifocal widespread disease precluding complete resection.

Radiotherapy can be used as a primary treatment or in the adjuvant setting. Recurrence rates from 0 to 60% have been reported, with no apparent differences between primary treatment and adjuvant therapy.

Systemic chemotherapy is used when surgery is not recommended, in cases of advanced disease, or in a neoadjuvant setting to reduce the tumor mass before surgical excision. Applied in combination with radiotherapy, it appears to improve responses and prevent recurrences, but the use of systemic chemotherapy alone requires further investigation.

Mohs' micrographic surgery has been associated with lower recurrence rates (8% to 28%) and less morbidity compared with standard surgical excision. It is typically performed in steps. A small scalpel is used to cut around the visible tumor. A very small surgical margin is used, usually with 1 to 1.5 mm of "free margin" or uninvolved skin. After each surgical removal of tissue, the specimen is processed, cut on the cryostat and placed on slides, stained with hematoxylin and eosin, and then read by the pathologist who examines the sections for cancerous cells. If cancer is found, its location is marked on the map (drawing of the tissue) and the surgeon removes the indicated cancerous tissue from the patient. This procedure is repeated until no further cancer is found.

Recent series with CO_2 laser treatment have reported recurrence rates similar to surgical excision but with significant post-treatment pain.

MELANOMA

Anal melanomas account for about 4% of anal canal tumors and less than 1% of all melanomas. Frequently it is not pigmented and does not have a macroscopically suspicious appearance. Management of anal melanoma remains a major challenge, and the prognosis is dismal. Despite the fact that most patients present with localized and apparently curable primary tumors, the mean survival time is only 2 years. Surgery is the treatment of choice because anal melanoma does not respond to chemoradiation. The extent of surgical resection (abdominoperineal resection vs local excision) does not seem to significantly impact outcome, as patients often die of distant metastases.

NEUROENDOCRINE TUMORS

Neuroendocrine neoplasms may occasionally occur in the anal canal. Most such tumors probably originate from neuroendocrine cells residing in colorectal type mucosa, although neuroendocrine cells are known to exist in ATZ mucosa as well. Because these lesions are often small, the treatment is typically a local excision.

MESENCHYMAL TUMORS

The most common types of mesenchymal tumors in the anal canal are smooth muscle tumors and gastrointestinal stromal tumors (GISTs). The treatment is typically just a local excision because the vast majority of them are small.

MALIGNANT LYMPHOMA

Primary lymphoma of the anal canal is rare. However, cases of both Hodgkin's disease and non-Hodgkin's lymphomas are reported. Patients with immunocompromise are particularly at risk. In this population, the lymphomas are mainly B-cell type and high grade. The treatment is chemoradiation.

SUGGESTED READINGS

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