CLINICAL IMAGE

A CASE OF METASTATIC ANAL CANCER WITH MULTIPLE CUTANEOUS LESIONS

Brooke A. Borgert, OMS-III[1]; Lindsay Tjiattas-Saleski, DO, MBA, FACOEP, FACOFP, Associate Editor[2]

[1]St. Luke's, Emergency Department, Columbus, NC
[2]Edward Via College of Osteopathic Medicine, Spartanburg, SC

CASE REPORT

A 56-year-old female presents with multiple painless but enlarging cutaneous nodules. The lesions rapidly developed on her face, torso, and legs (Figures 1 and 2). There was no associated warmth or fluctuance, and there did not appear to be any surrounding cellulitic changes or trauma. The patient denied any further systemic symptoms or similar previous episodes. Her past medical history was significant for: acid reflux, anxiety, depression, arthritis, constipation, hepatitis C, migraines, pancreatitis, sleep apnea, liver nodules, and anal squamous cell carcinoma (SCC). She had a 25-pack-year smoking history. Her past surgical history was significant for cholecystectomy and hysterectomy. She was also previously treated with combined chemoradiation for anal SCC.

About a year prior, the patient presented to the emergency department with a chief complaint of 6 weeks of constipation refractory to oral laxatives and suppositories. This was accompanied by lower abdominal and rectal pain with episodes of loose stool and blood per rectum. Upon physical exam, a perianal lesion was diagnosed as an external hemorrhoid and she was successfully treated for constipation and discharged. A month later, she presented again with alternating diarrhea, constipation, and pain per rectum. She was admitted for recurrent hematochezia and pain. An anal mass was observed and biopsied, with a final diagnosis of anal SCC with human papillomavirus (HPV) etiology. At computed tomography (CT) staging, the tumor was 7 cm in the craniocaudal dimension and 4 cm from the anal verge below the dentate line, and it was extending into the right ischioanal fossa with associated lymphadenopathy. Therapy included combined radiation and chemotherapy, but surgery was not indicated.

FIGURE 1:

Cutaneous nodule on face

FIGURE 2:

Cutaneous nodule on torso

CORRESPONDENCE:
Lindsay Tjiattas-Saleski, DO, MBA, FACOEP, FACOFP, Associate Editor
LTjiattassaleski@carolinas.vcom.edu

The authors have no conflicts of interest or financial disclosures.
We would like to acknowledge our kind brave patient.

QUESTIONS

1. What is the most likely diagnosis for the cutaneous nodules, given the history presented above?

a. Erythema nodosum

b. Lymphadenopathy

c. Metastases

d. Nodular lymphangitis

e. Sporotrichosis

Correct answer:
c. Metastases

When taking the patient's history and presentation into consideration, the lesions are most concerning for metastases. The lesions are not painful, do not appear to be infectious, and are fixed on exam. While this may have started as lymphadenopathy, the distant and pervasive spread is more indicative of a metastatic process. Furthermore, her exposure history to a fungus or bacteria to cause sporotrichosis, erythema nodosum, or nodular lymphangitis was not revealed in her history and is unlikely.

2: What is your next step in management?

a. Incision and drainage

b. Itraconazole

c. Oral antibiotics

d. Referral for biopsy

e. Topical steroid cream

Correct answer:
d. Referral for biopsy

Due to the clinical suspicion for metastases, a biopsy should be performed to characterize the histology and etiology of the tissue. Care should be taken when considering the region of the body that is being biopsied, history of present illness, and acuity of postbiopsy follow-up. In this case, a periauricular lesion was referred to an ENT for biopsy due to the sensitive nature of nearby neurovascular and bleeding risks, while the other lesions were referred to general surgery given the high suspicion for metastasis. There were no indications of infection in the area, so incision and drainage, antibiotics, or antifungals would not be appropriate. The lesions were painless, nonpruritic, and otherwise not impacting the patient at the time of presentation, so topical steroids are also not indicated.

DISCUSSION

This patient presented with a very uncommon and aggressive form of metastatic anal SCC caused by HPV 16. Anal cancer is a rare gastrointestinal cancer and is distinct from the more common colorectal cancers. Specifically, anal cancer makes up an estimated 3% of gastrointestinal cancers with 9760 new diagnoses a year.[1,2] Over 80% of anal cancer cases are due to SCC.[1] Squamous cells are ubiquitous in the skin and lining of hollow organs, like the anal canal below the dentate (or pectinate) line.[1] HPV infections are implicated for 93% of anal cancers causing SCC.[1] The strain of HPV can influence severity and especially devastating is HPV 16.[3,4] Screening and early diagnosis are pivotal to lessen the occurrence of anal cancer and its potential metastasis.

Rectal pain, bleeding, and pruritus are the most common presenting symptoms of anal cancer.[1] Anywhere from 50% to 80% of anal cancers are misdiagnosed due to their presentation mimicking benign processes like hemorrhoids, constipation, and diarrhea.[5-7] Therefore clinical suspicion should increase if these more benign diagnoses are refractory to initial standards of care. Women have higher rates of anal cancer than men (of the new cases per year, 3180 occur in men and 6580 in women).[2] While women are screened for HPV more frequently than men in a gynecologic setting with cervical Pap tests, anorectal screening should be included if the patient is a high-risk patient, positive for high-risk HPV types, or if cancer is suspected.[4] This can be done with an anal Pap test with cytology or digital rectal exam (DRE) if a lesion is observed.[2] Those who have a history of other cancers caused by HPV (cervical, oropharyngeal, penile, etc), have undermanaged HIV, are immunocompromised, practice anal receptive intercourse, or have received radiation to the pelvic area are at higher risk for developing anal cancer.[1]

Colonoscopy/anoscopy and biopsy serve to definitively diagnose anal cancer.[1] The location of the original lesion relative to the dentate line at the time of diagnosis determines patterns of lymph-node drainage and influences metastasis and treatment.[1] It is speculated that both lymphatic and hematologic systemic circulation can influence metastasis. Limited cases of metastasis from anal cancer are identified in the literature and include: the cranial bone and brain,[8-10] lymph nodes (including pelvic[11] and mediastinal locations[12]), paravertebral tissue,[13] liver,[14] and cutaneous nodules at the labia majora.[15] While SCC contributes to skin cancer as a primary lesion, metastasis to the skin is not typical.[16,17] To date, there were no documented cases of multiple, pervasive, metastatic cutaneous lesions in the literature.

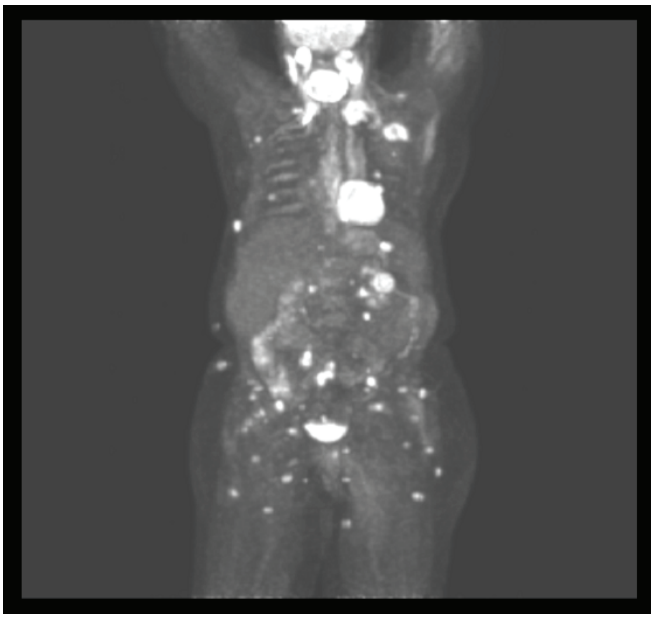
If anal cancer is diagnosed, there are standard treatment approaches that usually yield a positive prognosis and outcome for the primary lesions but success may be limited at later metastatic stages. There has been a transition away from surgical resection to utilizing anal-sparing chemoradiation therapy for initial treatment (either 5-fluorouracil and mitomycin C or 5-fluorouracil and cisplatin), which is often successful.[1,18] Little is known on the rate and timing of metastasis, with one study indicating 9% of anal cancers develop distant metastases.[19] Local recurrence is more common at 17%.19 For local recurrence, failure to respond to chemoradiation, or failure of local excision for superficial SCC, abdominoperineal resection (APR) should be considered.[1,18] Limited information exists for distant metastases due to its rare occurrence, but combined chemoradiation therapy is often reinitiated.[18,19] Recently, some developments in genome sequencing have improved survival and personalized treatment.[3] Though strides have been made to treat anal cancer, the HPV vaccine has made surmountable headway in prevention.

The ubiquity of HPV vaccination has lessened the overall occurrence of neoplasms caused by HPV. With regard to anal cancer, HPV is implicated in over 90% of cases with the p16 subtype the culprit for most infections.[1,18] The HPV vaccine is recommended for routine vaccination at age 11 or 12 years (but can be started as early as 9 years) and for everyone through the age of 26 years.[20] Some adults may opt for the vaccine up to the age of 45 years, based on discussion with their physician.[20] A recent study found that anal SCC rates are declining among vaccine-eligible adults compared to the incidence of disease in older populations, which continues to rise.[21]

When biopsied, the cutaneous lesions on this patient were revealed to be invasive moderately-to-poorly differentiated SCC involving the lateral and deep margins and invading the lymphovascular space. These were determined to be metastases from the primary lesion, and were invisible in sites ranging from the periauricular, lingual, inguinal, thigh, and back regions. A subsequent positron emission tomography (PET) scan, often used to assess the extent of disease when metastases are suspected, revealed innumerable cutaneous, subcutaneous, and muscular foci of F-fluorodeoxyglucose (FDG) activity indicating metastasis (Figure 3) with numerous areas of adenopathy. She was also profoundly hypercalcemic at this time. The patient began palliation and pain management as the lesions became exceedingly painful after biopsy and was properly referred to oncology for further chemotherapy and possible palliative radiation. During her course of diagnosis, remission, and recurrence, she had socioeconomic challenges to seeking care and was eventually lost to follow-up. The patient's disease sequela, comorbidities, and social determinants of health yielded a poor prognosis with a life expectancy of only about 6 months.

FIGURE 3:

PET scan revealing metastases



SUMMARY

Anal cancer is rare and its insidious symptoms can make diagnosis difficult. Moreover, mislabeling the diagnosis as colorectal cancer can impact reporting and subsequent prevalence and focus in medical literature. For family physicians, encouraging HPV vaccination, remaining vigilant to risk factors, and documenting accurate diagnoses can significantly lessen this disease burden on our patients.

REFERENCES

1. Young AN, Jacob E, Willauer P, Smucker L, Monzon R, Oceguera L. Anal cancer. *Surg Clin North Am*. 2020;100(3):629-634. doi:10.1016/j.suc.2020.02.007
2. American Cancer Society. Key statistics for anal cancer. Updated January 12, 2023. Accessed March 12, 2023. https://www.cancer.org/cancer/anal-cancer/about/what-is-key-statistics.html
3. Péré H, Vernet R, Pernot S, et al. Episomal HPV16 responsible for aggressive and deadly metastatic anal squamous cell carcinoma evidenced in peripheral blood. *Sci Rep*. 2021;11:4633. doi:10.1038/s41598-021-84110-2
4. Moscicki AB, Darragh TM, Berry-Lawhorn JM, et al. Screening for anal cancer in women. *J Low Genit* Tract Dis. 2015;19(3 suppl 1):S27-S42. doi:10.1097/LGT.0000000000000117
5. Anal Cancer Expanded Version. ASCRS. https://fascrs.org/patients/diseases-and-conditions/a-z/anal-cancer-expanded-version
6. Valvo F, Ciurlia E, Avuzzi B, et al. Cancer of the anal region. *Crit Rev Oncol Hematol*. 2019;135:115-127. doi:10.1016/j.critrevonc.2018.12.007
7. Bingmer K, Ofshteyn A, Stein SL. Delayed diagnosis of anal cancer. *J Gastrointest Surg*. 2019;24(1):212-217. doi:10.1007/s11605-019-04364-0
8. Benevento I, De Felice F, Bulzonetti N, et al. Successful treatment of anal canal cancer metastasis to the cranial bones: a case report and literature review. *In Vivo*. 2019;33(4):1347-1353. doi:10.21873/invivo.11610
9. Chihabeddine M, Naim A, Habi J, Kassimi M, Mahi M, Kouhen F. Anal cancer with atypical brain and cranial bones metastasis: about 2 cases and literature review. *Case Rep Oncol*. 2021;14(2):778-783. doi:10.1159/000516037
10. Rughani A, Lin C, Tranmer B, Wilson J. Anal cancer with cerebral metastasis: a case report. *J Neurooncol*. 2011;101(1):141-143. doi:10.1007/s11060-010-0218-5
11. Sakanaka K, Mizowaki T. A case report of a solitary pelvic mass proven to be a lymph nodal metastasis from anal cancer. *Case Rep Oncol*. 2020;13(1):164-169. doi:10.1159/000505969
12. Shenoy MA, Winnicka L, Mirsadraei L, Marks D. Anal cancer with mediastinal lymph node metastasis. *Gastrointest Tumors*. 2021;8(3):134-137. doi:10.1159/000514112
13. Ajala-Agbo T, Tang PT, Davidson TBU. Unilateral leg weakness and pain secondary to metastatic anal squamous cell carcinoma. *BMJ Case Rep*. 2012;12(7). doi:10.1136/bcr-2018-227563
14. Maulik S, Hande V, Engineer R, Mahantshetty U. Ten years and counting: survival in stage IV metastatic squamous cell carcinoma of anal canal following radical treatment. *J Cancer Res Ther*. 2020;16(suppl):S227-S229. doi:10.4103/jcrt.JCRT_118_18

15. Sakanaka T, Ishida Y, Mizowaki T. A case report of locally advanced anal cancer with solitary cutaneous nodular metastasis in the ipsilateral labia majora treated with definitive chemoradiotherapy. *Case Rep Oncol*. 2019;12(3):721-727. doi:10.1159/000503171

16. Hu SC, Chen GS, Wu CS, Chai CY, Chen WT, Lan CC. Rates of cutaneous metastases from different internal malignancies: experience from a Taiwanese medical center. *J Am Acad Dermatol*. 2009;60(3):379-387. doi:10.1016/j.jaad.2008.10.007

17. Saeed S, Keehn CA, Morgan MB. Cutaneous metastasis: a clinical, pathological, and immunohistochemical appraisal. *J Cutan Pathol*. 2004;31(6):419-430. doi:10.1111/j.0303-6987.2004.00207.x

18. Morris V, Eng C. Metastatic anal cancer and novel agents. *Surg Oncol Clin N Am*. 2017;26(1):133-142. doi:10.1016/j.soc.2016.07.008

19. Yellu M, Deeb A, Olowokure O. Overview of recent trends in the management of metastatic anal cancer. *World J Oncol*. 2015;6(1):311-315. doi:10.14740/wjon866w

20. Centers for Disease Control and Prevention. HPV vaccine recommendations. Updated November 16. 2021. Accessed March 12, 2023.

21. Berenson AB, Guo F, Chang M. Association of human papillomavirus vaccination with the incidence of squamous cell carcinomas of the anus in the US. *JAMA Oncol*. 2022;8(4):1-3. doi:10.1001/jamaoncol.2021.7652