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Author

Kirimis, Evangelia

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CLINICAL VIGNETTE

Human Papilloma Virus and Metastatic Cancer

Evangelia Kirmis, M.D.

A 67-year-old female noted an enlarged mass in her right groin. In retrospect, the mass was likely there for months, but she never thought much about it until she noted a mass jutting out while doing a yoga pose. Medical exam showed a golf ball-sized right inguinal mass. There was no other noted lymphadenopathy. Excisional biopsy was done, and pathology showed metastatic non-keratinizing squamous cell carcinoma (SCC). The cancer was strongly and diffusely positive for p16. Altogether, these findings suggested a primary cervical cancer. Interestingly, the patient had had a recent gynecologic exam that was unremarkable. Pap smears had always been unremarkable and repeat was negative for malignancy. Furthermore, she remained human papilloma virus (HPV) negative. Colonoscopy was recently done and negative except for hemorrhoids. She presented for discussion of treatment.

She was otherwise asymptomatic and with minimal other medical problems. She was married for 40 years. Her family history was notable for a sister with melanoma. Vital signs and physical exam were now unremarkable except for the noted right inguinal surgical site. She was not certain how thorough the inspection of her anal area was during her colonoscopy.

Given no clear primary malignancy, she proceeded with Positron Emission Tomography/Computed Tomography (PET/CT), which showed post-surgical changes in the right inguinal area. There was focal hypermetabolism in the anorectal junction. In review with radiology, the findings were non-specific and could be related to irritation from bowel movements.

While the patient's lymph node biopsy suggested a primary cervical cancer, the strong p16 expression, which is a surrogate for HPV, was discordant with her prior HPV-negative Pap smears. Thus, she was referred to surgery for anoscopy and full exam. Exam did not show evidence for malignancy, but anal Pap smear showed dysplastic cells and was positive for high risk HPV 16. Blind anal biopsies showed at least anal squamous cell carcinoma in situ (AIN III) in three of four quadrants and foci highly suspicious for invasive carcinoma in the right posterior quadrant. Thus, this patient's case was consistent with an HPV-positive anal squamous cell cancer with metastatic disease only in the right inguinal node.

Squamous cell cancer of the anus is a rare disease but makes up about 80% of all anal cancers.^{1,2} It is linked to HPV infection.¹ It is more frequently seen in females and occurs usually after 60 years old.¹ Certainly the patient above is consistent with this epidemiology. The incidence of anal SCC has increased over

time and felt to be related to increasing HPV infection and changing sexual practices.^{1,2} Accordingly, the patient above was found to be HPV-positive from her anal swab albeit HPV-negative by cervical Pap smear. Other risk factors include anal intercourse, immune function (particularly related to human immunodeficiency virus infection), and smoking.¹ She did not have any such risk factors. Prior meta-analyses indicate that like cervical cancer, upwards of 80% of anal SCC are associated with HPV, most commonly HPV16.^{1,2} Precancerous lesions have been recognized in the pathogenesis to invasive disease.¹ As such, high-risk patients can engage in screening similar to Pap smears for cervical cancer.¹ As was seen in the patient presented, she had evidence of carcinoma in situ in all biopsy samples.

Inguinal node involvement is associated with increased risk of recurrence and poorer prognosis.¹ However, sentinel lymph node biopsies have never shown definitive benefit for management, and thus, are not standard of care.¹

There are several notable points in the above case. Her presentation was interesting given a sole lymph node involved on exam without any clear primary lesion on imaging. The pathology from that lymph node suggested that the most likely etiologies were cervical cancer, anal cancer, and head and neck cancer given the non-keratinizing SCC and strong p16 positivity. Given no other metastatic disease, the metastasis to the inguinal area would be uncharacteristic of a head and neck cancer. Pap smear was unremarkable, and she remained HPV negative. Thus, the pathology did not correlate well with cervical cancer despite the report. There was no anal lesion noted on exam, and the patient had no high-risk features to suggest a risk for anal cancer. However, it was reasonable to pursue more pathology given the possibility of a hidden, small lesion. Her anal swab supported blind biopsies given the positivity for HPV16. Interestingly, even though the biopsies suggested low bulk primary invasive disease, she already had metastasis to her inguinal node. This case highlights how important it is to evaluate the pathologic findings thoroughly and look for an occult primary when the pathology and imaging are discordant.

The literature did not indicate other reports of HPV-negative cervical Pap smears with such strongly HPV-positive anal disease. Given the patient's low risk sexual history, one would expect diffuse positivity through the anogenital area, but was clearly not the case here.

In the end, concurrent chemoradiation treatment was recommended with fluorouracil and mitomycin with curative intent. The patient proceeded with treatment and was in the midst of treatment at the time of this publication.

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