Title

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CLINICAL VIGNETTE

Mistaken Identity: Penile Cancer in the Setting of Bladder Carcinoma, Potential Confusing Histopathologic Diagnoses

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As an old medical adage states, "when you hear hoofbeats, think horses, not zebras." While this phrase has been around for years, to teach that in medicine the most likely cause of an ailment is usually the true cause and not the most unlikely, all possibilities should be appropriately evaluated. In clinical situations, as in the one presented below, one misevaluation can risk great danger to a patient.

A 64-year-old Asian male who resided in California was diagnosed with early stage left sided ureteral urothelial cell carcinoma for which he -underwent left nephroureterectomy for definitive management. He received no adjuvant therapy and subsequently developed a new noninvasive urothelial cell carcinoma in the bladder. After transurethral resection of bladder tumor (TURBT), he received intravesical immunotherapy with bacillus Calmette-Guérin (BCG) as standard of care. Due to recurrence of noninvasive disease, further BCG with interferon therapy was given. Follow-up surveillance cystoscopy initially demonstrated chronically inflamed bladder mucosa but subsequently revealed urothelial cell carcinoma with squamous differentiation with vascular invasion. The bladder urothelial cell carcinoma invaded the subepithelial connective tissue (lamina propria). Despite the high grade nature of this lesion (grade 3 of 3), the muscle invasion was not identified in the biopsies. Options for his treatment at that point including definitive surgical management were being considered by the patient.

While visiting the Philippines, the patient developed an episode of priapism lasting several days prompting medical evaluation. A local urologist noted a mass involving the corpus cavernosum and recommended biopsy. The pathology was reported to be squamous cell carcinoma, and penectomy was recommended for what was thought to be a new primary penile tumor. He was alarmed at this recommendation and decided to return to the United States for further evaluation.

At UCLA, the biopsy slides from the Philippines were examined and compared with his original urothelial carcinoma. The UCLA pathologist reported that the penile lesion was most consistent with urothelial carcinoma with squamous cell differentiation and therefore was clearly metastatic and not primary in nature, as previously diagnosed. The outside physician was apparently not aware of the patient's urinary tract cancer, which lead to an incorrect assumption based on this tumor's location and the expectation that a primary penile tumor would be squamous cell. The variant histopathology of true urothelial carcinoma with squamous cell differentiation was not included in the differential diagnosis.

After re-evaluation, radiation therapy was recommended to treat this penile metastasis, along with chemotherapy with gemcitabine and cisplatin due to the rapid progression to metastatic disease.

This case illustrates how easily it may be for a physician to be misled about a patient's diagnosis if a full medical history and actual histopathology of his bladder cancer diagnosis were not considered carefully.

The urothelium lines the urinary tract from the renal pelvis down the ureter into the bladder, with the urethra ending at the distal end of the penile urethra in males. At the penile urethra, a transition point toward squamous epithelium is then seen on the surface of the external penis[1]. Penile carcinomas, despite their rarity, are known to be typically squamous cell carcinomas with little variant histology. On the other hand traditional urothelial cell carcinomas (previously known as transitional cell carcinomas) have a characteristic appearance, which is very different from pure squamous cell carcinoma. However highly under recognized, the atypical variant form of urothelial carcinoma contains squamous type differentiation. In fact, there are several variant histologies associated with urothelial carcinoma. Common variant histopathologies include the following three groups: 40% pure urothelial cell carcinoma, 30-40% squamous and adenocarcinomas,

and 5% small cell carcinomas[2,3]. Of the 30-40% squamous and adenocarcinomas, 20% are made up of squamous carcinomas, and 10% adenocarcinoma cells[4]. The non accurate diagnosis that was made in the Philippines may have been due to the extreme similarity in morphology of those two entities as well as due to lack of the original slides from his bladder tumor for them to compare. The urothelial cell carcinoma with squamous cell differentiation, depending on the extent of involvement, may appear similar to the pure squamous urothelial cell carcinoma as well as a penile squamous cell carcinoma; however, their clinical behavior may be distinctly different[1,5,6].

Bladder cancer and ureteral cancer were known entities for this patient; however, it is a type of carcinoma that typically starts in the lining of the bladder or other part of the urinary tract called the urothelium (also known as transitional cell epithelium)[7,8]. There are now over 70,000 new cases each year in the United States[3,9]. They are typically classified in two ways: papillary tumors that have a wart-like appearance and attach to the stalk or nonpapillary (sessile) tumors that are flat and are much less common[5]. Nonpapillary bladder carcinomas tend to be more invasive, or spread to surrounding tissues, resulting in worse clinical outcomes.[5] Certain risk factors are associated with the development of bladder cancer, with the main cause having yet to be discovered[10]. Cigarette smoking, the most significant risk factor, and lesser causes—such as chemical exposure at work, chemotherapy, or even radiation treatment—increase the risk for developing bladder cancer[10]. Regarding risk factors, there are also other possible etiologies such as prior health conditions, including bladder infection (schistosomiasis), which, if long term, may cause irritation that can lead to certain kinds of bladder carcinomas[10-12]. The pathologic grading of urothelial cancer is classified as low grade or high grade based upon the degree of nuclear anaplasia and architectural abnormalities[5]. The extent of cancer invasiveness is further determined based on thickness of invasion depending on the extent of bladder wall penetration—e.g., into lamina propria, muscularis propria, or even through the bladder wall into the surrounding adipose tissue—including perivesicular structures, such as the rectum or prostate[5]. A major clinicopathologic distinction is initially made between muscle invasive versus nonmuscle invasive disease mainly because of ultimate different clinical behavior[5]. Noninvasive tumors are usually confined to the bladder and in general are not life threatening, as opposed to muscle invasive tumors, which acquire the ability to spread widely and potentially place a patient's life at risk as they tend to grow rapidly[5].

Penile carcinomas, on the other hand, are a relatively uncommon type of cancer. They occur in about 1 of every 100,000 males, making about 7,000 cases a year worldwide (1,600 cases in the United States), accounting for 20% of cancers (in men) in parts of Africa, Asia, and South America[9,11]. This type of tumor is well differentiated and affects the subepithelial connective tissue[1]. The prognosis of this malignancy correlates with the stage at the time of the diagnosis. Overall, the five-year survival rate for all stages of penile cancer is about 50%. About 95% of penile malignancies are squamous cell carcinoma[1,6]. The other histological subtypes are basal cell carcinoma, melanoma, sarcoma, and metastatic lesions (such as urothelial carcinoma like in our case)[1] . Due to psychosocial barriers, most men delay seeking treatment, and with hesitation they inconsistently seek follow-up care, which also delays diagnosis and appropriate treatment[13]. Numerous men fear demasculinization of their identities if they receive the necessary treatment. This often results in a personal internal conflict between the will to survive for longer with a nonfunctional penis or living a shorter life with a functional penis[13].

At the time of the writing of this case report, the patient has received four of six planned cycles of the platinum doublet with partial response based on imaging, however, his prognosis is poor given the metastatic nature of his disease.

This case illustrates how easily it may be for a physician to be misled about a patient's actual diagnosis, if a full medical history and actual histopathology of his bladder cancer diagnosis were not considered carefully.

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