RESIDENT'S CORNER

Loss of e-cadherin and retinoblastoma genes in a case of urothelial carcinoma with scrotal metastasis

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Cutaneous metastases from urologic cancers are very uncommon, usually represent widespread metastatic disease and are associated with a very poor prognosis. They may occur in 1% of patients with urologic malignancies, most commonly from kidney, followed by bladder and prostate tumors. In this report, we describe a case of urothelial carcinoma with metastases to the scrotum treated with platinum based chemotherapy with a durable complete response lasting more than 14 months. Molecular profiling revealed deleterious mutations in e-cadherin and retinoblastoma genes, suggesting their possible role in the pathogenesis of cutaneous metastases. Further studies are needed to validate this observation.

Key Words: e-cadherin, retinoblastoma, urothelial carcinoma, scrotal metastases

Introduction

Cutaneous metastases are rare in visceral malignancies. They can present with a variety of symptoms similar to other common, benign skin diseases such as skin induration, small papules or larger skin lesions. Cutaneous metastasis may precede the diagnosis of malignancy, and early recognition and diagnosis is important. A review by Mueller and colleagues found cutaneous metastases in 2.9% of patients with solid malignancies, while the incidence in urologic malignancies was around 1.3%.[1]

Since the scrotum represents less than 1% of body surface area, it is a very rare site of cutaneous metastatic disease with less than 30 reported cases in the literature. Most cases of scrotal metastases were from the genitourinary tract, three of which were from urothelial carcinomas.[2] Scrotal metastases are almost always an indicator of advanced metastatic disease and carry a very poor prognosis. Of the patients with reported survival data, the median interval between the diagnosis of scrotal metastasis and death was only 2 months (range 1-11 months, mean = 3.8).[2] Several theories have been proposed to explain the underlying mechanism involved in cutaneous metastases which include direct extension, tumor seeding at a previous incision site, lymphatic or hematogenous spread; however, the exact mechanism is still unclear and still needs to be elucidated.[3]

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Case report

Our patient is an 82-year-old Caucasian man, non-smoker, with a past medical history of hyperlipidemia, coronary artery disease and osteoporosis who was found to have microhematuria on routine urine analysis in December 2008. His family history was significant for a maternal aunt with breast and ovarian cancer. Once the hematuria was discovered, he underwent a cystoscopy followed by transurethral resection of the newly discovered bladder mass. Pathology revealed a muscle invasive high grade urothelial carcinoma. Subsequently, a robotic-assisted cystoprostatectomy with ileal loop urinary diversion and extensive pelvic lymph node dissection with the removal of 45 lymph nodes was performed. He was found to have a T2aN0M0 high grade muscle invasive urothelial carcinoma that was 2.6 cm in greatest dimension with negative surgical margins. The patient elected not to have any adjuvant chemotherapy or radiation therapy and was followed closely with imaging studies.

In March 2013 he presented for a follow up with the complaint of a firm mass he had just recently noticed on his right scrotal skin. He denied any scrotal pain, dysuria, hematuria, penile discharge, fever or weight change. Physical exam was unremarkable except for a firm, non-tender, non-erythematous multi-lobulated nodular lesion that was 2 cm x 2 cm located on the posterior right portion of his scrotum. Complete blood cell count and serum biochemistry tests were normal except for a hemoglobin of 12.9 gm/dL and platelets of 128 K/mm^3. The scrotal mass was removed and gross examination of the specimen revealed a 3.1 cm x 1.3 cm ellipse of white-tan, hairbearing skin with underlying soft tissue (2.9 cm x 1.2 cm with a depth of 3.1 cm). No lesions were identified on the skin. The subcutaneous tissue was diffusely firm. Sectioned specimen revealed a white, glistening, fibrotic cut surface. No necrosis or hemorrhage was identified. Surgical margins were positive. Microscopic examination revealed soft tissue containing pleomorphic tumor cells infiltrating the dermis in a single file pattern without involvement of the epidermis, Figure 1A and 1B. Immunostaining was positive for AE1/AE3, CK7 and weakly positive for CK20, Ker903 and p63, Figure 1C, while negative for CD45, PSA and S100. Even though tumor cells were focally positive for p63 and Ker903; in the presence of a history of high grade urothelial carcinoma, a metastatic urothelial carcinoma was favored. Immunostains for GATA and uroplakin were not performed.

A restaging PET CT scan was done which showed no evidence of metastatic disease beyond the scrotum. Due to positive skin margins, our patient was referred to his urologist for surgical re-excision. In the interim, he developed several new lesions on the scrotum and perineum, Figure 2A. Due to rapid progression of his scrotal lesions, surgery was aborted and systemic therapy was pursued. Since patients with scrotal metastases have had only limited success with conventional chemotherapy, molecular profiling (FoundationOne, Foundation Medicine, Inc. Cambridge, MA, USA) was offered to determine if there was a genetic target available to exploit. Interestingly, testing revealed loss of e-cadherin (CDH1-Q641*) and retinoblastoma (RB1) genes with no therapeutic that specifically targets those genomic alterations. Therefore, our patient was offered palliative chemotherapy and was started on gemcitabine 1000 mg/m^2 and cisplatin 70 mg/m^2. This was discontinued after one cycle due to significant hematologic toxicities and he was switched to carboplatin AUC 4 and gemcitabine 800 mg/m^2. He tolerated four cycles of this regimen with complete resolution of his skin lesions, Figure 2B. As of now, 14 months later, he is not receiving any chemotherapy and his cancer is still in complete remission.

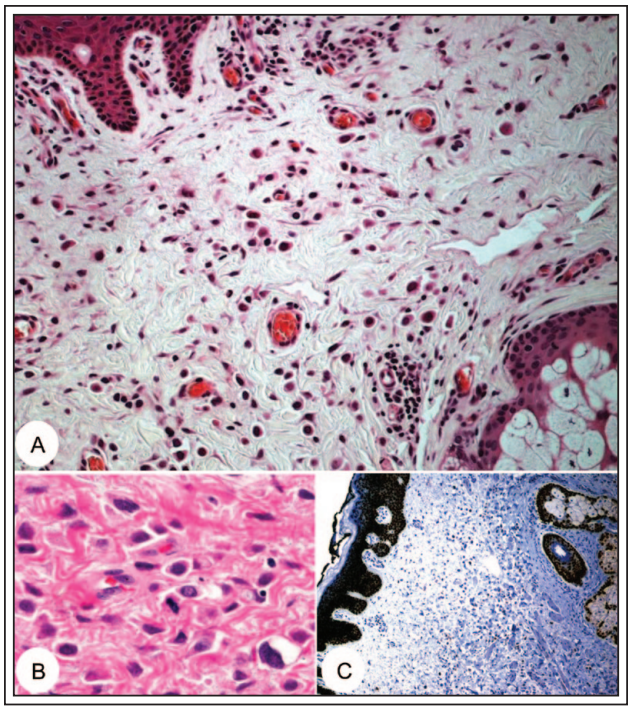

Figure 1. H&E staining of scrotal skin biopsy shows tumor cells in a single file pattern present in the dermis and absent in the epidermis at 200X magnification **A)** Higher magnification (400X) shows a pleomorphic appearance of tumor cells **B)** Staining for p63 was only weakly positive **C)** At 100X magnification.

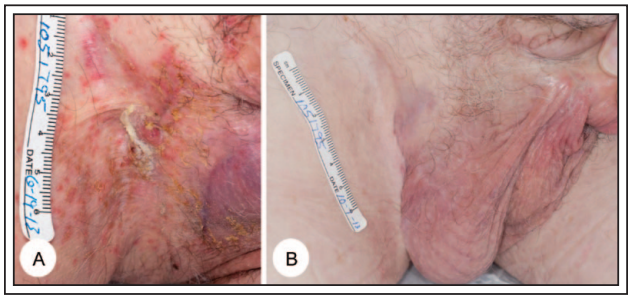

Figure 2. While awaiting surgical reexcision of his right scrotal mass, our patient developed multiple new lesions **A)** Surgery was aborted and the patient received platinum based chemotherapy with complete resolution of scrotal metastatic disease **B)**.

Discussion

Our patient was initially diagnosed with invasive high grade urothelial carcinoma in 2008 and underwent cystoprostatectomy with ileal loop urinary diversion. He declined adjuvant chemotherapy and radiation therapy. Five years later he presented with a scrotal metastasis as the only site of metastatic disease. A review of the literature showed only a limited number of cases being successfully treated with chemotherapy. A variety of therapies have been tried including radiation or different chemotherapy combinations: cisplatin + etoposide, fluorouracil + leucovorin, hexestrol + cortisone acetate, diethylstilbestrol and MVAC (methotrexate + vinblastine + doxorubicin + cisplatin). Only three patients with scrotal metastases survived more than 1 year. One patient was treated with penile scrotoplasty and was still living 2 years later, another 79-year-old man with urothelial carcinoma of the bladder was treated with MVAC chemotherapy and was asymptomatic for 15 months, while the third patient, a 65 year-old man with squamous cell carcinoma of the anal canal, was treated with a variety of antineoplastic agents and was still alive 13 months later, although with progressive disease.[2]

Cutaneous metastases occur in up to 5% of patients with solid tumors and can sometimes present as the initial sign of malignant disease. Since the scrotum represents less than 1% of body surface area, it is a very rare site of cutaneous metastatic disease. The molecular mechanism by which cutaneous metastases develop remains elusive; however, it is well known that cancer progression is attributed to the accumulation of genetic mutations in cancer cells.[4] The epithelial-to-mesenchymal transition (EMT) is one of the pivotal events in cancer progression and it is characterized by loss of epithelial phenotype and acquisition of migratory characteristics. E-cadherin complex has been shown to be an important factor in the EMT and an important event in the pathogenesis of cancer. E-cadherin and the associated catenin complex have a key role in cell adhesion and they are an important suppressor of cell invasiveness. Loss of e-cadherin leads to decreased cellular adhesion, eventually causing cell migration and metastasis.[5-7] RB1 encodes the retinoblastoma protein (Rb1), a tumor suppressor protein and negative regulator of the cell cycle. Loss of Rb1 expression was found to play a role in the progression of urothelial cancers and is associated with an advanced disease and poorer survival.[8,9] A study by Arima et al demonstrated that Rb1 is an upstream regulator of e-cadherin and other EMT-related molecules, playing a key role in the EMT inhibition by up-regulating the expression of e-cadherin. Consequently, Rb1 loss is associated with cancer invasion and metastasis.[10] Molecular profiling in our patient revealed loss of e-cadherin (CDH1-Q641*), which results in truncation of the protein within the extracellular domain and loss of the transmembrane domain which is required for binding to CTNND1, PSEN1, and catenins. This mutation leads to an inactivated e-cadherin complex.[6] The other detected mutation was deletion of RB1, which encodes the retinoblastoma protein (Rb1), a tumor suppressor and negative regulator of the cell cycle that leads to uncontrolled cellular replication. It is not clear whether concomitant e-cadherin and retinoblastoma mutations are random events or if they are responsible for the development of cutaneous metastases.

In summary, cutaneous metastases are relatively uncommon. There are only a few dozen cases of metastatic lesions to the scrotum, which is almost always associated with a grave prognosis. Our patient had durable complete response to platinum based chemotherapy; he likely did very well because he only had minimal disease burden. Results of molecular profiling of the tumor suggested that losses of e-cadherin and RB1 genes are not mutually exclusive and might be part of progression pathway in cutaneous metastases ("double hit hypothesis"). Further studies are needed to validate this observation. □

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