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Case Report
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Malignant Melanoma to the Testicle Presenting as Left Scrotal Swelling

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Abstract

Objective: Present the rare presentation of metastatic melanoma to testicle presenting as scrotal swelling.

Case Report: We present the case of an 85-year-old male with a previous diagnosis of non-metastatic melanoma who presented with several months of scrotal swelling.

Results: Histopathologic evaluation of testicular mass confirmed the presence of metastatic melanoma of the testis.

Conclusion: Though rare, malignant melanoma to the testicle should remain in the differential diagnosis in patients presenting with testicular masses or scrotal swelling, especially if their past medical history is positive for cutaneous melanoma.

Keywords: Malignant melanoma; Testicular mass; Testicular cancer; Orchiectomy; Urologic oncology

Introduction

As the third most common cutaneous malignancy, Melanoma often spreads from subcutaneous skin to visceral organs. In 2021, there were an estimated 106,000 new invasive Melanoma cases with over 7,000 deaths [1]. Melanoma's risk of spread depends on the primary lesion, with the metastasis being categorized as local, regional, or distant. Literature finds that a gradual transition between these three categories occurs in that respective order, with distant being the final stage.

To our knowledge, there are 9 documented cases of metastatic malignant melanoma with spread to the testicles. It is essential that primary disease be ruled out, which can be seen typically in men aged 20 to 30 whereas metastatic melanoma growth would be seen in men 40+. Germ cell tumors such as seminomas and non-seminomas must be considered, especially if the patient is younger. Additionally, lymphomas and melanomas should be included in a differential despite their rarity. Tumors that do metastasize to the testicles are most commonly from the prostate at 35%, the lung at 19%, and then melanoma and the colon tying at 9% [2].

In the few documented cases, the typical presentation appears to be a middle-aged or an elderly man presenting with pain and swelling of the testicle [3]. These growths are often unilateral and may have a past medical history of melanoma identified from a skin biopsy [4]. They are often palpable masses that can appear with gray nodules and black-blue macules [5]. In addition to a rapidly growing testicular mass, there are cases where it has metastasized to the supraclavicular nodes [3].

Case Presentation

We present the case of an 85-year-old male with a several months history of left testicular swelling. Physical exam revealed a firm left testicle without erythema, discoloration, necrosis, or tenderness to the scrotum. Physical exam was negative for inguinal lymphadenopathy.

The patient had a history of melanoma (Breslow thickness greater than 1.0 up to 2.0 mm in thickness, without ulceration, pathologic stage pT2a) of the right buttock's status post wide local excision two years prior to presenting with testicular swelling. At that time, PET scan and sentinel lymph node biopsy was negative for metastasis.

During the initial work up, scrotal ultrasound revealed a diffusely heterogeneous, nodular

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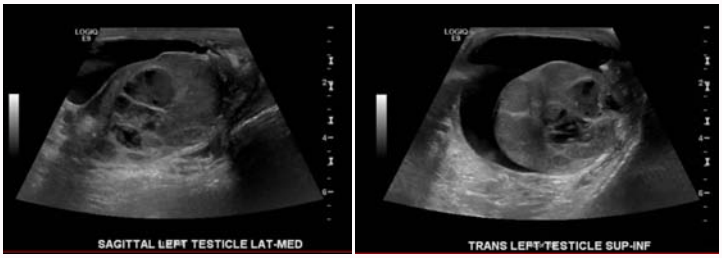

Figure 1 and 2: Diffusely heterogeneous, nodular appearance of the left testicle.

Figure 3: 7.5 cm tan, ill-defined mass, involving nearly the entire testis. Foci of hemorrhage, necrosis, cystic changes identified.

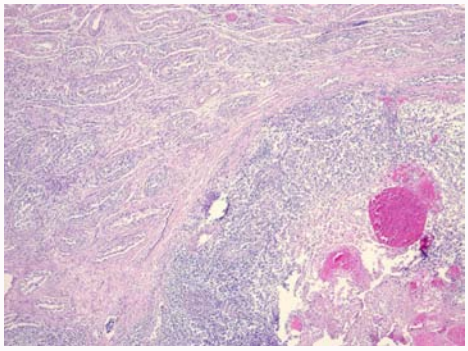

Figure 4: H&E 40x - tumor with necrosis at the lower right of image Upper left of the image: Seminiferous tubules some with residual active spermatogenesis but others showing intratubular spread of tumor.

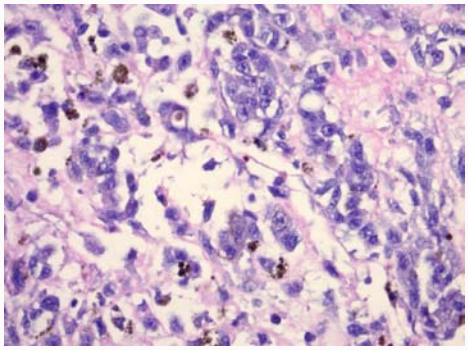

Figure 5: H&E 400x - deposits of dark brown pigment appear compatible with melanin pigment and when seen in context of a malignant neoplasm can suggest a diagnosis of melanoma.

appearance of the left testicle that was suspicious for malignancy (Figure 1, 2). Tumor markers were within normal limits; Alpha Fetoprotein (AFP) was <3 ng/mL (reference range <11 ng/mL), beta hCG was <1 IU/L (reference range 0-3 IU/L), and lactate dehydrogenase was 165 U/L (reference range 135-225). Malignant work up with CT scan of the chest, abdomen, and pelvis revealed a stable lung nodule but was negative for other masses or lymphadenopathy. PET scan was performed, which was negative for metastasis.

The patient underwent a left radical inguinal orchiectomy. During pathologic evaluation, sectioning of the testicle revealed a 7.5 cm × 5 cm × 4 cm tan, ill-defined soft mass encompassing almost the entirety of the testis (Figure 3). Some areas of hemorrhage and necrosis were identified in the mass. The mass did not appear to grossly extend into the paratesticular structures. Low power H&E staining photomicrograph demonstrated tumor with areas of necrosis and intratubular spread of tumor (Figure 4). High power H&E staining photomicrograph demonstrated tumor cell cytomorphology, which includes moderate amounts of cytoplasm and vesicular nuclei with variably prominent nucleoli. Deposits of dark brown pigment appeared compatible with melanin pigment and when seen in context of a malignant neoplasm can suggest a diagnosis of melanoma (Figure 5). On immunohistochemical evaluation, tumor cells were positive for SOX10, HMB45 (human melanoma black), Mart1/Melan-A and S100, common markers used to confirm melanoma, and negative for cytokeratin AE1/AE3 and CD45. The brown staining observed in the tumor cells is considered a positive result, which supports the diagnosis of melanoma. The blue hematoxylin counterstained cells, including seminiferous tubules at the left of the image, are considered negative for the antigen of interest (Figure 6). A melanoma hotspot NGS panel, which includes BRAF, NRAS and KIT, was performed and revealed no mutations in any of the three hotspots.

Following radical orchiectomy, the patient was evaluated by Medical Oncology and discussed at Melanoma Tumor Board. It was felt the pulmonary nodule seen on the CT scan of the chest was slow growing and had been present for several years prior or testicular swelling, making it less likely to be related to the patient's diagnosis of metastatic melanoma. Medical Oncology discussed the possibility of recurrence of disease with the patient, though recurrence is difficult to quantify given the rarity of metastatic melanoma to the testicle. They offered the patient one year of adjuvant therapy with anti-PD-1 therapy in an effort to reduce the risk of recurrence. However, given the patient's past medical history of heart failure, chronic kidney disease and his age, the patient elected for observation with surveillance CT Chest/Abdomen/Pelvis (CAP) 3-months after radical orchiectomy.

Three month follow up CT CAP showed new nodules along the left anterior pararenal fascia and right buttocks concerning for recurrent/metastatic disease. The patient followed up with Medical Oncology at

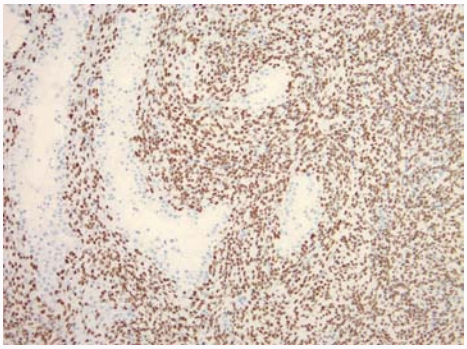

Figure 6: 100x immunohistochemical stained slide for SOX10nuclear transcription factor, a common marker used to confirm melanoma. Brown staining represents nuclear expression of SOX10 in the melanoma cells which grow between seminiferous tubules (left side of image).

that time and the decision was made to begin Nivolumab/Relatimab, a combination of Nivolumab which is a PD-L1 inhibitor and a LAG-3 pathway inhibitor which increases the T-cell mediated response. Approximately 3 months after initiating Nivolumab/Relatimab, follow up CT scans showed significant worsening retroperitoneal disease involving the left paraspinal area with encasement of the left ureter and mild left hydronephrosis (Figure 7), significant worsening left inguinal mass (Figure 8), hepatic metastasis (Figure 9) and pulmonary nodule suggesting progression of metastatic disease. The plan at that time was to continue Nivolumab/Relatimab and undergo stereotactic radiation therapy to the liver. A few weeks after undergoing radiation to the liver, the patient was admitted to the hospital with Diabetic Ketoacidosis and encephalopathy. During this admission the patient and family elected to transition to comfort care only. The patient was discharged to hospice and passed away shortly after, 11 months after initial evaluation by urology for left testicular swelling.

Diagnosis

Following an orchiectomy, histopathological evaluation usually demonstrates poorly cohesive, large, epithelioid cells with prominent nucleoli involving the interstitium and possibly the seminiferous tubules [2]. Appropriate immunohistochemical studies are usually necessary for the identification of the origin of metastatic tumors. Primary tumors of the testis that may mimic a metastatic melanoma include Leydig cell tumors and lymphoma. Immunohistochemical stains useful in the diagnosis of metastatic melanoma include S-100, HMB-45, Mart1/Melan-A and SOX10. These markers are typically

Figure 8: Follow up CT abdomen/pelvis showing enlarging left inguinal masses.

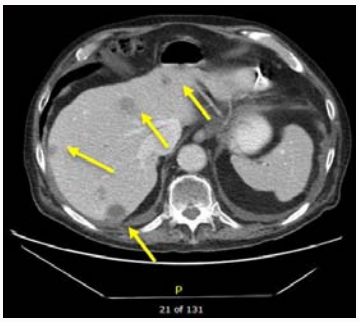

Figure 9: CT abdomen pelvis showing hepatic mets.

ordered in a panel and positivity of one or more of these markers in the tumor cells would provide supportive evidence of metastatic melanoma. With the testicles being considered a distant area, the appearance of malignant melanoma here indicates a particularly poor prognosis which is often first seen during an autopsy.

Discussion

In the United States, melanoma is the fifth most common cancer diagnosed with an estimated 106,000 new cases in 2021 - more than a 320% increase since 1975 [6]. UV exposure, immunosuppression, and family history are just some of the primary risk factors for melanoma. Despite an increase in incidence, there has been a significant decrease in the overall mortality due to the various chemotherapy options.

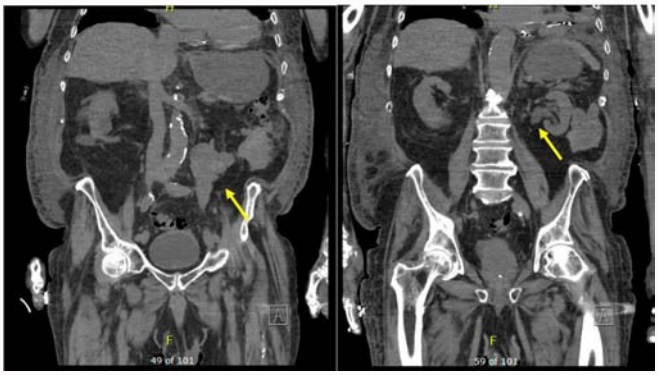

Figure 7: Follow up CT abdomen/pelvis showing large left retroperitoneal mass causing left hydronephrosis.

As a malignant cancer, melanoma often metastasizes to the skin, lungs, liver, and occasionally the small bowel. However, current review of literature reveals that there is an extremely rare occurrence of testicular metastasis secondary to melanoma [7]. With the testicles being considered a distant area, the appearance of malignant melanoma here indicates a particularly poor prognosis which is often first seen during an autopsy. It is not likely to ascertain a proper diagnosis until an orchiectomy is done due to the presentation. Like what is detailed above, a proper diagnosis is made through histopathology. The workup of this malignancy was first made by sonography, which revealed a heterogeneous composition. The benefits of sonography in this instance are a high specificity and sensitivity, capable of differentiating a cystic lesion from a mass, and provides a location of the anomaly [8]. These methods are consistent with other documented cases [2].

Due to the hypermetabolic state of melanoma, a PET scan is recognized as an important path of the work up [9]. Our testing did not reveal any significant uptake. In addition to the imaging modalities, tumor markers were identified *via* immunohistochemical testing and a Melanoma Hotspot Next-Generation Sequencing (NGS). The value of the latter is in identifying oncogenes BRAF, NRAS, and KIT. Half of all melanoma mutations are associated with a BRAF mutation [6]. Furthermore, NRAS and KIT are commonly altered in patients with UV radiation resulting in high cumulative sun damage [10].

BRAF (B-RAF proto-oncogene, serine/threonine kinase) encodes a serine threonine kinase as part of the MAPK/ERK pathway. Mutations in this gene are the most commonly identified mutations in melanoma, as well as other cancers [11-13]. NRAS (Neuroblastoma RAS viral (v-RAS) oncogene homolog) mutations appear in 20% of melanomas and are mutually exclusive with BRAF mutations [14-16]. Additionally, NRAS mutations have a worse prognosis than BRAF tumors.

Conclusion

Histopathologic analysis following radical orchiectomy in patients with metastatic melanoma to the testicle reveals poorly cohesive, large, epithelioid cells with prominent nucleoli involving the interstitium and possibly focally the seminiferous tubules [2]. A Melanoma Hotspot Next Generation Sequencing (NGS) Panel can be performed, as seen in our case presentation, to aid in diagnosis and prognosis of metastatic melanoma to the testicle. The Melanoma Hotspot NGS Panel can interpret several melanoma-associated genes at once. In particular, the Melanoma Hotspot Panel analyzes driver oncogenes BRAF, NRAS, and KIT, classic markers and anti-cancer drug targets for melanoma [17]. The absence of mutations in these driver oncogene targets may suggest a better prognosis [18]. Studies have found that patients diagnosed with melanoma that had mutations at BRAF, NRAS, or KIT tended to be more aggressive forms of melanoma [18-20].

With the testicles being considered a distant area of metastasis, the appearance of malignant melanoma here indicates a particularly poor prognosis which is often first seen during an autopsy. In an instance where a prior orchiectomy has been performed, physicians consulted a PET-scan and a sonogram, of which the latter demonstrated a heterogeneous lobulated mass replacing the testicle [2]. Sonography is the preferred method due to its ability to distinguish various lesions as well as determine vascularity.

Though rare, malignant melanoma to the testicle should remain in the differential diagnosis in patients presenting with testicular masses or scrotal swelling, especially if their past medical history is positive for cutaneous melanoma [2].

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