Case Report: Primary pure angiosarcoma of the testis

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Angiosarcoma is a rare and aggressive, malignant neoplasm of endothelial-cell origin. A primary angiosarcoma originating in the testicle is extremely rare, with only five previous cases reported in the current literature. We report a case of primary, pure angiosarcoma of the testis in a 63-year-old patient with no history of previous chemotherapy or radiation therapy. By histology, the tumor was a high-grade spindle cell neoplasm, arranged in sheets and poorly-formed vascular channels. The tumor cells were positive for vascular markers (CD31, CD34) by immunohistochemical staining. No evidence of a germ cell component was seen by morphology, immunohistochemistry, or molecular genetic studies. This finding is unique in that it is one of only three reported cases of primary angiosarcomas of the testicle without a germ cell precursor or component.

testicle | angiosarcoma | germ cell tumor | testicular neoplasm | sarcoma

Angiosarcoma is an aggressive soft-tissue sarcoma that is composed of malignant endothelial cells of vascular or lymphatic origin. Angiosarcomas are rare tumors, comprising only 1% of soft tissue sarcomas (1). These tumors are found primarily in the head and neck followed by breast, the extremities, and trunk (2). Angiosarcomas are frequently associated with prior radiation therapy and chronic lymphedema, particularly in the breast (2). They can also arise in organs, most commonly liver, as well as the heart, spleen, and lung. Angiosarcoma of the testis is exceedingly rare, with only scattered case reports in the literature.

Case Report

A 63-year-old male presented with an enlarged right testicle. He reported a history of firmness in the testicle for over 10 years. However, over the preceding eight months, the testicle had rapidly enlarged to 11 cm in size. Pre-operative work up with an ultrasound and staging CT scan showed a solid lesion occupying the testicle and no evidence of metastases, respectively. β-HCG and AFP levels were within normal limits. The patient did not have a history of chronic lymphedema or prior radiation therapy. Furthermore, there was no known exposure history to vinyl chloride, thorium dioxide, arsenic, radium, or anabolic steroids. He underwent an inguinal right radical orchiectomy without incident. During the procedure, several lymph nodes were discovered at the level of the internal inguinal ring. These lymph nodes were palpably abnormal and were subsequently removed for examination. Although not standard protocol, the patient's anatomy lent itself to node sampling.

Materials and Methods

Light microscopic images were obtained using standard H&E staining protocols on paraffin-embedded tissue sections. Immunohistochemistry analysis involved using antibodies to: CD31, CD34, pan-keratin, calretinin, AFP (alpha fetoprotein), and PLAP (placental alkaline phosphatase) with appropriate positive and negative controls. Additionally, Fluorescence In situ Hybridization (FISH) Analysis for Chromosome 12p was performed.

Pathology

A gross depiction of the testicle following right radical orchiectomy is shown in Figure 1. The testis measured 11 x 8.5 x 7 cm and weighed 514 grams. The cut surface of the testis was red-tan to black and hemorrhagic, alternating with areas of white, solid fibrotic tissue. No residual normal appearing testicular tissue was noted. The spermatic cord and epididymis appeared uninvolved by tumor. Four pelvic lymph nodes were also received separately.

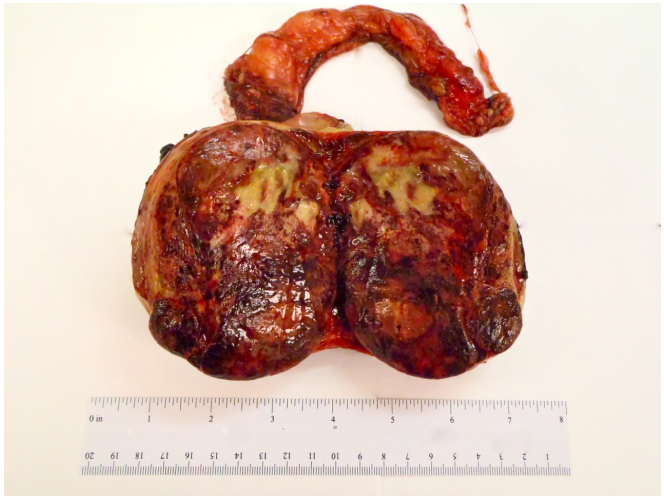

Figure 1: The orchiectomy specimen covered with a smooth red-tan intact tunica vaginalis. The cut surface revealing areas of hemorrhage, necrosis, and white, solid fibrotic tissue. No residual testicular tissue is grossly identified. The adjacent spermatic cord and epididymis was grossly uninvolved by tumor.

Microscopic examination revealed that the tumor was composed of a high-grade spindle cell neoplasm. The tumor had biphasic growth, including areas with large vascular spaces (Figure 2) and more solid areas filled with spindle cells and smaller slit-like vascular channels (Figure 3). The tumor cells showed marked nuclear pleomorphism, and frequent mitoses. Extensive geographic necrosis

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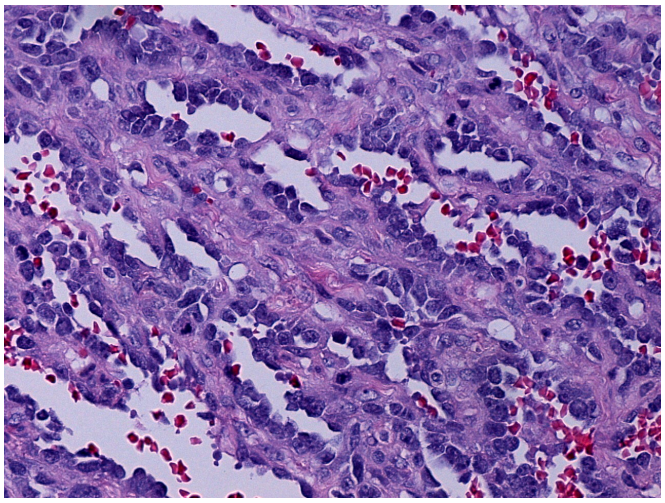

Figure 2: Microscopic examination showing high-grade spindle cells with enlarged atypical nuclei and plump endothelial cells lining large vascular spaces. There are a number of mitotic figures present.

was present. The tumor replaced the entire testicular parenchyma but did not invade the tunica vaginalis, epididymis or spermatic cord. Despite extensive sampling, no areas of either seminomatous or non-seminomatous germ cell neoplasia were seen. The four separately received pelvic lymph nodes were negative for tumor.

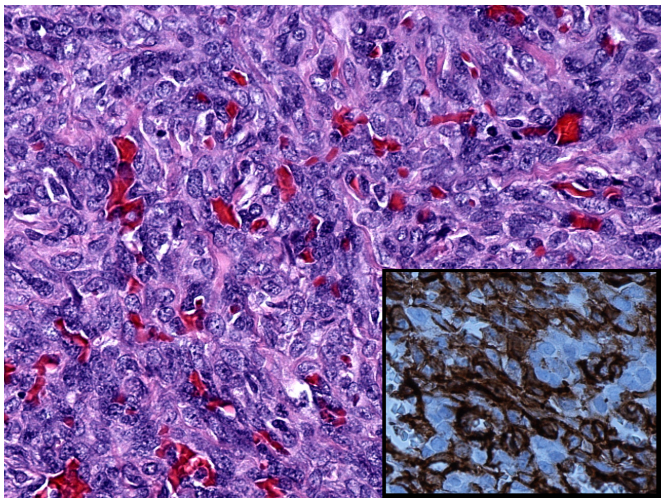

Figure 3: Microscopic examination revealing more solid areas with increased cellularity and compact vascular channels intervening between sheets of spindle cells. No residual testicular parenchyma is present. The inset shows immunohistochemical analysis with tumor cells reacting strongly for CD 31 (PECAM-1) membrane receptors.

Immunohistochemistry revealed that the tumor cells were positive for CD31 (Figure 3) and CD34, supporting the endothelial origin of the tumor. The tumor cells were negative for pan-keratin, calretinin, AFP, and PLAP by immunohistochemical stain.

FISH analysis was performed. Interphase FISH probes for 12p11.21 and 12centromere were used, and no evidence of isochromosome 12p was observed.

Discussion

Angiosarcomas of the testicle are very rare tumors. To our knowledge, there are only a total of five cases previously reported in the English medical literature (3). Angiosarcoma of the testicle is morphologically similar to that seen in other locations.

Angiosarcomas can be varied in cytology and overall architecture depending on the degree of differentiation. The cytologic variation of angiosarcomas includes epithelioid, spindled, or polygonal cells. The architecture has been described as vasoformative, sieve-like, kaposiform, or solid (1). In general, well-differentiated tumors show relatively well-formed vascular channels compared to poorly differentiated tumors, where the malignant endothelial cells become crowded and multilayered, becoming solid with only poorly formed, slit-like vascular spaces. Typical nuclear features include hyperchromasia, marked pleomorphism, and prominent nucleoli (3, 4). A single tumor may show a spectrum of differentiation, architecture, and cytology, such as was seen in this case (Figures 2,3). Despite extensive sampling, no areas of germ cell differentiation were seen.

Immunohistochemical analysis further supported the diagnosis. CD31 is an endothelial marker with high sensitivity and specificity for angiosarcomas (5). In addition, markers of germ cell origin, such as PLAP and AFP, were negative.

Chromosome 12p alterations are one of the earliest changes in germ cell tumors and are present in virtually all testicular tumors of germ cell origin (6). The lack of isochromosome 12p in this case further supports our interpretation of a pure angiosarcoma without a germ cell component. A review (3) of the 5 previously reported testicular angiosarcomas suggested two groups of patients with different age ranges. The first group, which includes 3 of the reported 5 cases, consists of young patients (average age of 21) that have angiosarcomas arising from teratomas or other germ cell neoplasms. The second group, which includes 2 of the 5 reported cases, consists of elderly patients (average age of 76) with angiosarcomas of non-germ cell origin. Our case of a 63-year-old male, with a primary angiosarcoma of the testicle with non-germ cell origin is congruent with the second group described.

Angiosarcomas are aggressive tumors, having an overall 5-year survival of 35% in all sites (2). Treatment involves complete surgical resection with wide margins due to the multifocal and invasive nature of the tumor. High-dose radiation over a wide area is typically employed following surgical excision except in cases of radiation-induced angiosarcomas. Adjuvant chemotherapy has no demonstrated survival advantage. However, for metastatic disease, the primary treatment is chemotherapy, using mainly doxorubicin or a taxane (2, 7).

In the testicle, the primary treatment for angiosarcomas has been radical orchiectomy. Of the five previously reported cases, each underwent complete resection with negative margins, and two received adjuvant chemotherapy, both of whom were young patients with germ cell tumor-associated angiosarcomas. Of the five previous patients, three were alive and without disease with an average of 17 months follow up, one died a month after diagnosis from a stroke, and one had metastatic disease to the lung at four months follow-up (3). Our patient recovered well from his surgery, but presented with symptoms of back and hip pain within three months of surgery. The patient's pre-operative CT scan was negative for metastasis but his planned three-month post-operative PET and CT scan were positive for widely metastatic disease in the bones, which accounted for his symptoms. His performance status rapidly declined and, consequently, he was not a candidate for chemotherapy. Also, he was not interest in pursing systemic chemotherapy. At most recent follow up, he had been placed in hospice care.

We are aware of only five previously reported cases of angiosarcoma of the testicle which share the morphologic and immunohistochemical features of angiosarcomas in other locations. In the rare cases reported in the literature, angiosarcoma is associated with germ cell tumors in young men while it arises de novo in older men, with

our case falling into the latter category. In summary, we report a case of pure angiosarcoma of the testicle, an exceedingly rare diagnosis. Angiosarcoma is an aggressive malignancy with poor outcomes in most locations. However, due to its rarity, it is difficult to speculate on expected outcome in testicular angiosarcoma.

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