Case Report

Epitheloid hemangioendothelioma of the urinary bladder: A case report of a rare entity

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ABSTRACT

Epithelioid hemangioendothelioma (EHE) is a rare, often multifocal, intermediate-grade vascular sarcoma arising from the endothelial cells. Their behavior is intermediate between hemangioma and conventional angiosarcoma. Their rarity and unpredictable clinical behavior result in our still limited understanding and treatment options for this variety of tumors. Molecular diagnostic tools like the presence of WWTR1-CAMTA1 fusion have been developed to aid this challenging diagnosis. There is no definitive consensus on the management of patients with this disease and no commonly accepted treatment strategies have been found to be effective, particularly in the metastatic setting. When possible, surgery with clear margins should be considered in case of localized disease. Here, we not only present such a rare case of EHE of the urinary bladder but also provide a comprehensive discussion on the present treatment modalities offered, as found through a thorough search of the published studies. Finally, more studies are required to establish a standard of care for this rare entity

Key words: Epitheloid hemangioendothelioma, Sarcoma, Urinary bladder

Epithelioid hemangioendothelioma (EHE) is a rare, often multifocal, intermediate-grade vascular sarcoma arising from endothelial cells [1]. Most commonly, it arises in the liver, lungs, and other soft tissues. Epitheloid vascular neoplasms are characterized morphologically by the presence of epithelioid endothelial cells. They can be divided into three distinct varieties: epithelioid hemangioma, EHE, and epithelioid angiosarcoma [1]. According to the most recent World Health Organization classification [2], EHE is considered a malignant vascular tumor similar to an angiosarcoma, although with a better prognosis [3]. The EHE was first described by Weiss and Enzinger in 1982 as a borderline or low-grade neoplasm [4]. Since then, there have been only a few reported cases of this entity arising from the urinary bladder in reported literature worldwide. Their rarity and unpredictable clinical behavior result in a limited understanding of the treatment options.

Here, we present such a rare case of EHE of the urinary bladder which had a very unconventional presentation with a considerable discussion on the present treatment modalities offered found through a thorough search of the published studies and case reports worldwide.

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CASE REPORT

A 42-year-old gentleman, with no prior history of hematuria, underwent laparoscopic hernioplasty for the left inguinal hernia. Intraoperatively, a few suspicious left femoral lymph nodes were found and biopsied. Post-procedure, the patient developed hematuria and gradual swelling of the left inguinal region extending to the lateral aspect of the thigh. Histopathology of the biopsied femoral node came as poorly differentiated carcinoma and this is when the patient first presented to us.

An initial workup was carried out with a routine examination of the blood and urine and contrast-enhanced computed tomography (CECT) of the chest, abdomen, and pelvis. CECT of the abdomen revealed a large neoplastic lesion in the left wall of the urinary bladder with bilateral inguinal and retroperitoneal lymphadenopathy. There was no evidence of any liver or lung nodules.

The femoral biopsy slides were concurrently submitted for review at our center. As the tumor cells were positive for pan-cytokeratin but negative for multiple epithelial markers, the possibility of a vascular tumor with epithelioid morphology was considered. The tumor cells showed reactivity for CD31, CD10, CD34, ERG, and FLI1, and hence, a diagnosis of metastatic hemangioendothelioma was made.

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After a multidisciplinary tumor board discussion, the patient was taken up for transurethral resection of the bladder tumor (TURBT) and resection of the mass. Intraoperatively, the patient was found to have multiple diffuse papillary solid sessile space-occupying lesion involving the left lateral wall, posterior wall, and base of the urinary bladder and extending deep into the muscle layer, not amenable to complete trans urethral resection.

Post-procedure, the patient had a progressive increase in his left inguino scrotal and left lower limb swelling. An ultrasound Doppler of the bilateral lower limb revealed a large conglomerated lymph nodal mass with internal necrosis in the bilateral femoral region with compression. There was no evidence of thrombosis or infiltration of vessels with nodal mass.

Biopsy from the TURBT chips showed a tumor composed of atypical epithelioid cells with pleomorphic nuclei, prominent nucleoli, and eosinophilic cytoplasm (Fig. 1a). Given the unconventional finding in a urinary bladder mass, a detailed immunohistochemistry (IHC) with a comparison from the tissue of the first biopsy from the nodal mass was done. In IHC, the tumor cells were positive for pan-CK, CD 31 (Fig. 1b), CD 10, CD 34, ERG (Fig. 1c), and FLI1, thus recapitulating the findings in the lymph node biopsy. This is when the tumor arising from the urinary bladder was confirmed to be one of the few reported cases of a urinary bladder epitheloid hemangioendothelioma with nodal metastasis.

We then started him on systemic therapy with vascular endothelial growth factor (VEGF) inhibitor bevacizumab in combination with paclitaxel and Peg GSF in a weekly regime. He is presently ongoing treatment and is planned for assessment after three cycles.

DISCUSSION

Epithelioid hemangioendothelioma, being rare cancer, is a diagnostic dilemma since there is no definitive consensus on the management and no commonly accepted treatment strategies have been found to be effective, particularly in the metastatic setting.

Characteristic histopathologic features of EHE include plump cells with eosinophilic hyaline cytoplasm, angiocentric location, cytoplasmic vacuoles representing primitive vascular lumina, cells arranged in cords, a chondromyxoid matrix, and papillary tufts of plump cells within lymphovascular spaces [5]. Confirmatory evidence is described as erythrocytes within cytoplasmic vacuoles or primitive tumor-cell lined channels which mirror the primitive vasoformative character of EHE and immunohistochemical evidence of endothelial differentiation [1]. IHC is invariably used for confirmation of such rare entities and its widely accepted that CD31 is the most specific and sensitive endothelial marker [6]. Recently, a new hallmark of EHE has been identified: the presence of WWTR1-CAMTA1 fusion may serve as a useful molecular diagnostic tool in challenging diagnoses [7].

When possible, surgery with clear margins should be considered in case of localized disease [5]. Radiotherapy has no place in the management of these tumors. Similarly, chemotherapy has variable responses [8]. Alternatively, embolization of the feeding vessel to cause a spontaneous regression of vascular tumors has been tried. Interferon α-2b (IFNα-2b) has shown some positive impact in suppressing vascular tumors of the brain, soft tissue, and liver [9,10]. However, its beneficial effects in organs such as the bladder remain unknown. The expression of VEGF and VEGF receptor demonstrated in EHE and angiosarcoma has paved way for its use in such tumors [11]. More recently, an experience with a selective drug targeting the mammalian target of the rapamycin pathway has been reported. Among 12 patients treated with sirolimus, as a single agent, they reported one response and six stabilizations proving that sirolimus resulted in a high proportion of possibly long-lasting tumor responses [12].

Drugs such as doxorubicin, vincristine, and fluorouracil have been reported to have achieved disease stabilization, while regression has also been seen with doxorubicin alone. In one of the largest published data [13] on treating EHEs at various sites, the most used chemotherapeutic regimen was paclitaxel, which even though had a symptomatic benefit for some patients, did not achieve any objective response. In the same study, anthracyclines showed similar results, with the best response being stable disease. Six patients in this cohort were treated with celecoxib, which works by inhibiting cyclo-oxygenase, involved in the inflammation process, a critical component of tumor progression [14].

Specifically, in the case reported by Geramizadeh *et al*. from Iran, of EHE of the urinary bladder with possible infiltration of the sigmoid colon in a 4-year-old boy, the patient was treated with pre-operative chemotherapy [15]. When no tumor response was observed and symptoms of bowel obstruction developed, near total with Sigmoidectomy and Hartmann procedure for the involvement of the sigmoid colon. Postoperatively, considering

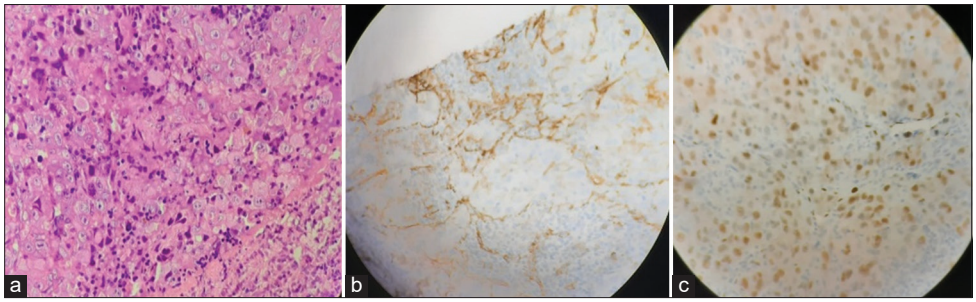

Figure 1: (a) Histopathological examination of the tumor cells showed atypical epithelioid cells with pleomorphic nuclei, prominent nucleoli, and eosinophilic cytoplasm; IHC showed tumor positivity for (b) CD 31 and (c) ERG

the possibility of the early recurrence, the patient was kept on IFNα-2b therapy. They provided a follow-up record of 6 months postoperatively where the patient has been reported to have faired satisfactorily with no evidence of tumor recurrence. In another reported case by Gupta *et al*., for an EHE urinary bladder, the patient was fortunate to have a disease limited to the trigone of the bladder with no muscle invasion which was amenable to complete resection by TURBT. They have provided the report of a 1-year follow-up post-resection without recurrence in absence of any form of local or systemic therapy [16].

In our case, we faced the challenge of finding the patient in an advanced stage where complete resection was no longer feasible. The disease is bulk on presentation with gross nodal involvement and the rapidly deteriorating patient's general condition mandated a trial of systemic therapy and reassessment with close follow-up of his hematological parameters and general condition.

CONCLUSION

Epithelioid hemangioendothelioma still remains one of the rarely reported neoplasms worldwide. In EHEs of the urinary bladder, surgery, if feasible, has the best outcome. In advanced diseases, the role of medical therapy remains unclear. However, with advances in molecular diagnostics, it is possible to classify EHE more reliably and objectively: the novel fusion gene WWTR1-CAMTA1 has been identified as a hallmark of the disease and can be used to establish the diagnosis in challenging cases. Finally, more studies are required to establish a standard of care for this rare entity and specifically why, reporting of such cases becomes significant.

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